BMC Public Health

RESEARCH

Open Access

Trends and projections of Non-Hodgkin lymphoma burden (1990–2040): a global burden of disease 2021 analysis

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Abstract

Background Non-Hodgkin lymphoma (NHL) is a common type of lymphoma. These vary geographically and within specific areas. A comprehensive and precise assessment of the global burden of NHL is important for the forward-looking planning and implementation of health policies.

Methods This study used data from the 2021 Global Disease Burden (GBD) study. We examined trends in disease burden in non-Hodgkin lymphoma patients using indicators including the incidence, prevalence, deaths, and disability-adjusted years of life (DALY), as well as the age-standardized incidence rate (ASIR), age-standardized prevalence rate (ASPR), age-standardized mortality rate (ASMR), and age-standardized DALY rate (ASDR). Temporal trends in NHL risk factors from 1990 to 2021 were analyzed. Joinpoint regression was used to determine the average annual percentage change (AAPC) in the age-standardized rate. The Bayesian age-period-cohort (BAPC) model was used to predict the age-standardized mortality and DALY rates by 2040.

Results In 2021, the NHL's global age-standardized incidence rate (ASIR) was 7.1 per 100,000 people. From 1999 to 2021, there was a downward trend in ASMR and ASDR of NHL (AAPC = -0.6 and -0.8, respectively), but ASIR and ASPR of NHL showed an upward trend (AAPC = 0.3 and 1.2, respectively). According to the socio-demographic index (SDI), the ASIP and ASPR of NHL were higher in regions and countries with higher SDI. The study also found an increase in ASMR and ASDR associated with high body mass index (BMI) in NHL. In addition, it is predicted that the global ASIR and ASPR will continue to show a slow upward trend in the next 2040, whereas ASMR and ASDR will gradually decline.

Conclusion Non-Hodgkin lymphoma (NHL) remains a formidable public health challenge; however, different regions and socioeconomic statuses have different trends. A more aggressive, individualized intervention strategy is needed based on dynamic changes. Simultaneously, close international collaboration is essential to advance improvements in NHL management, including strengthening diagnostic and treatment strategies, strengthening healthcare infrastructure, expanding access to high-quality healthcare services, and strengthening public health education.

Keywords Non-Hodgkin lymphoma, 2021 Global burden of disease, Epidemiology, Death, DALYs, Projections

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Introduction

In recent years, the incidence of malignant lymphoma has notably increased, resulting in it being among the top ten most prevalent cancers globally [1]. Non-Hodgkin lymphoma (NHL), a hematologic malignancy derived from lymphocytes [2], accounts for 90% of all malignant lymphoma cases [3]. NHL not only affects patients' quality of life, but also shortens their life expectancy. Managing these diseases requires significant financial resources, and often places a significant financial burden on patients, their families, and society. As the global population ages, NHL prevalence continues to increase. However, the burden of NHL varies by region and within a region. A comprehensive and accurate assessment of the global burden of disease caused by NHL is essential. According to the latest GLOBOCAN 2020 estimates, NHL accounted for an alarming number of 544,000 new cases and 260,000 deaths globally in 2020. This translates to NHL, contributing to 2.8% of all cancer cases and 2.6% of all cancer-related deaths worldwide [4]. NHL exhibits remarkable heterogeneity, with each distinct subtype intricately linked to various risk factors [3]. Numerous studies have demonstrated a significant association between individual factors, environmental factors (e.g., pesticides, organic solvents, ionizing radiation, and exposure to low-frequency electromagnetic fields), and the presence of HIV/AIDS [5].

Given the high incidence, heterogeneity, and complex landscape of treatment modalities, NHL imposes a formidable burden on both the patients and society. Moreover, the economic implications of NHL vary significantly, with costs differing not only by subtype but also across geographical regions [6]. Shen et al. revealed a compelling trend in the global incidence rate of NHL, which steadily increased from 1990 to 2019; in contrast, the death rate associated with NHL remained relatively stable during this period [7]. The burden of NHL fluctuates significantly across countries and regions, and evolves over time. Notably, in recent years, Western countries have reported a relatively favorable 5-year survival rate of approximately 70% in patients with NHL. This positive outcome stems from the integration of advanced treatment strategies, including chemotherapy, radiotherapy, immunotherapy, and targeted therapy, which have significantly improved patient outcomes [8]. Therefore, it is necessary to reassess the current trends and burdens of NHL. Although previous studies have investigated the epidemiological trends of NHL, many have been constrained by the use of outdated data or a narrow scope limited to specific countries. With advances in medical technology and demographic changes, NHL prevalence has increased. Outdated data do not accurately reflect the current morbidity, mortality, and epidemic trends in NHL. In addition, prognostic evaluation models need to be built and optimized based on the latest clinical data and biological characteristics, and outdated data may lead to the failure of prognostic evaluation models. These studies may have overlooked critical aspects, such as age-based disease distributions, nuanced age trends at the national level, and the intricate interplay between lifestyle and metabolic risk factors [9, 10], all of which are vital for a comprehensive understanding of NHL. Our study overcomes these limitations by employing the latest data, expanding its scope, and employing advanced research methods to provide a more comprehensive and accurate analysis.

This study aimed to capitalize on the most recent 2021 Global Burden of Disease Study (GBD 2021) data to conduct a comprehensive analysis of NHL at the global, regional, and national levels. Specifically, we examined the age-standardized incidence rate (ASIR), age-standardized prevalence rate (ASPR), age-standardized mortality rate (ASMR), and age-standardized disability-adjusted life years (DALYs) rata (ASDR). Furthermore, this study investigated the temporal trends in these metrics, stratified by age, sex, and geographic location, to gain a nuanced understanding of how NHL varies across populations. In addition, projections for the future, such as forecasts of ASIR, ASPR, ASMR, and ASDR associated with NHL up to 2040, are needed.

Methods

Data sources

The data for this study were sourced from the estimated 2021 Global Burden of Disease (GBD) dataset, an exhaustive compilation that offers comprehensive insights into the global and regional burdens of 369 diseases, injuries, and 88 risk factors across 204 countries and territories from 1990 to 2021. All anonymized data were accessed and downloaded via the Global Health Data Exchange (GHDx) platform (http://ghdx.healthdata.org/gbd-results-tool). For this follow-up analysis, we downloaded the following comprehensive datasets: 1). A comprehensive array of annual age-specific NHL data from 1990 to 2021, spanning global, regional, and national levels. These include detailed counts of cases, patients, deaths, and DALYs along with their corresponding crude and age-standardized rates (ASRs); 2). population data of global, regional, and national age groups from 1990 to 2021; 3). ASR data pertaining to relevant risk factors attributed to NHL collated at global, regional, and national levels for both 1990 and 2021; and 4). Socio-demographic index (SDI) data were used to assess the impact of socioeconomic factors on disease burden.

As the data utilized in this study were sourced from a publicly available database, ethical approval and informed consent were not required.

Statistical analysis

Global and regional burden analysis

The age-standardized rate (ASR) (per 100,000 people) was calculated based on the world standard population reported in the 2021 Global Burden of Disease (GBD) Study. To analyze the global distribution of and regional differences in NHL burden, we generated global maps and regional comparative analyses. The data were aggregated by geographical regions as defined by the GBD study, and maps were created via R (version 4.4.2) with the `ggplot2` and `sf` packages to visualize the distribution of disease burden.

Temporal trend analysis

To evaluate temporal trends in the incidence, prevalence, death, and DALY associated with NHL from 1990 to 2021, we employed a sophisticated joinpoint regression analysis [11]. The analysis was performed via the `Joinpoint` R package. Rigorous calculations were conducted to quantify the trends in the annual percentage change (APC) and overall average annual percentage change (AAPC) of the parameters under study. The annual percent change (APC) and its 95% confidence interval (CI) were calculated using the geometrically weighted mean of the various annual percentage change values in the regression analysis, and were used to estimate temporal trends in age-standardized incidence rate (ASIR), age-standardized prevalence rate (ASPR), age-standardized mortality rate (ASMR), and age-standardized DALY rate (ASDR). The average annual percentage change (AAPC) is a summary of trends over a predetermined fixed time interval and a weighted average of APCs that describes the average APC over a multiyear period [12].

Population analysis

Population-level analyses including age, sex, and specific subpopulations were conducted to explore the distribution of NHL across different demographic groups. The data were stratified by age group (e.g., 65–69 years, 70–74 years, etc.) for both males and females. Statistical analyses were performed using R (version 4.4.2), and the results were visualized using the `ggplot2` package.

Socio-demographic index (SDI) analysis

The GBD 2021 study used the socio-demographic index (SDI) as a composite measure of socioeconomic status, which is strongly associated with health outcomes. The SDI combines per capita income, educational attainment, and total fertility rate (TFR) to assess a country's socio-demographic development. According to the GBD 2021 study, there are five levels of SDI: High SDI (> 0.81), Medium High SDI (0.70–0.81), Low to Medium SDI (0.61–0.69), Low to Medium SDI (0.46–0.60), and Low SDI (< 0.46) (https://ghdx.healthdata.org/record/global-burden-disease-study-2021-gbd-2021-socio-demographic-index-sdi-1950%E2%80%932021). To investigate the intricate relationship between the SDI and NHL burden, we conducted a detailed analysis by calculating the SDI-specific disease rates. The `dplyr` and `ggplot2` packages in R were employed for data manipulation and visualization.

Risk factor analysis

We analyzed the comprehensive data provided by the GBD 2021 study to dissect the intricate factors contributing to the NHL burden. This study aimed to identify and evaluate the key risk factors that significantly impact disease prevalence and associated burden. A comprehensive analysis was conducted to assess the attributable DALYs of each risk factor. The `forestplot` R package was used to create forest plots that display the contributions of various risk factors to the overall disease burden.

Average annual percentage change (AAPC) analysis

The AAPC of NHL was calculated to measure the average rate of change in the disease burden over time. This analysis was conducted via the `segmented` R package, and the results are presented as the percentage change per year with 95% confidence intervals.

Bayesian Age-Period-Cohort (BAPC) model for forecasting

To predict the future burden of NHL, we utilized the Bayesian Age-Period-Cohort (BAPC) model [13]. The BAPC model is a method applied in epidemiology and biostatistics to analyze the relationship between incidence and time. It uses samples and prior information to obtain unique parameter estimates, showing better coverage and precision than other prediction methods, as demonstrated in previous studies [14]. BAPC models combine past data and probability distributions to allow us to estimate future patterns of disease progression, taking into account age, period, and cohort effects, and are used to describe and predict cancer burden trends. To implement the BAPC model for predicting the future burden of NHL disease, we leveraged the capabilities of the `INLA` and `BAPC` packages within R (version 4.4.2), which allow us to forecast the incidence and prevalence of the disease through 2040. Owing to the incorporation of age, period, and cohort effects, the BAPC model offers a holistic and nuanced understanding of the intricate dynamics that shape the future burden of NHL.

All the statistical analyses and data visualizations were conducted via R (version 4.4.2). We generated descriptive statistics for all pivotal variables and presented the results in a clear and concise manner, accompanied by 95% uncertainty intervals (UIs). All figures were dramn by the JD-GBDR, developed by Jingding Medical Technology.

For trend analyses, p-values < 0.05 were considered statistically significant.

Results

Global, regional and National NHL incidence and age-standardized incidence rate in 1990, and 2021

As shown in Table 1, there were 255,667 new NHL cases worldwide in 1990, and the age-standardized incidence rate (ASIR) per 100,000 people was 3.1 cases. By 2021, the number of new NHL cases worldwide is 604,554, and the ASIR was 7.1 per 100,000 people. The global average annual percentage change (AAPC) for ASIR was 0.3 (0.2,0.4), with the largest increase in ASIR recorded in Andean Latin America (AAPC: 3.3 (3.2,3.5)). NHL occurs worldwide. There were significant differences between the locations. There was an approximately 5-fold difference between the highest and lowest incidence rates. Figure 1-A highlights the regional differences in ASIR, with Andean Latin America having the highest incidence (ASIR = 20.2) and Central Asia having the lowest incidence (ASIR = 2.5) in 2021. In addition, the SDI was significantly associated with NHL incidence. Figure 2-A further illustrates the increasing trend of NHL ASIR from 1990 to 2021 in high-SDI regions, while low-SDI regions show a more modest increase.

Global, regional and National NHL prevalence and age-standardized prevalence rate in 1990, and 2021

In 1990, there were 1,035,772 NHL cases worldwide, and the age-standardized prevalence rate (ASPR) was 22.3 cases per 100,000 people. By 2021, the number of global NHL cases was 2,919,051, and the ASPR was 34.3 per 100,000 people; the global AAPC for ASPR was 1.2 (1.0,1.5), with the largest increase in ASPR recorded in Andean Latin America (AAPC: (5.4 (5.2,5.6)) (Table 2). Globally, the prevalence of NHL varies widely around the world, with very significant differences between the regions with the highest and lowest prevalence. Figure 1-B highlights regional differences in ASPR, with Australasia having the highest prevalence (ASPR = 110.7) and Central Sub-Saharan Africa having the lowest prevalence (ASPR = 5.4) in 2021. Figure 2-B further illustrates the increasing trend of NHL ASPR from 1990 to 2021 in high-SDI regions, while low-SDI regions show a more modest increase.

Table 1 Global incidence of NHL in 1990 and 2021 and the corresponding average annual percent change (AAPC)

Location	1990 (95% UI)		2021 (95% UI)		AAPC
	Number	ASIR	Number	ASIR	
Global	255667.8(242749.3-272800.9)	6.1(5.8–6.5)	604554.1(558229.2-648746.2)	7.1(6.6–7.7)	0.3(0.2,0.4)
High-middle SDI	52907.0(50218.7-56507.1)	5.2(4.9–5.5)	135074.2(121911.4-148399.6)	7.4(6.7–8.1)	1.1(1.0,1.2)
High SDI	125897.1(121016.2-128829.7)	11.9(11.4–12.1)	247508.2(225875.0-263943.7)	13.0(12.0-13.7)	-0.1(-0.3,0.2)
Low-middle SDI	22203.4(19093.1-26688.2)	2.8(2.4–3.4)	56154.0(49728.9-69678.9)	3.5(3.1–4.4)	0.7(0.6,0.7)
Low SDI	13097.6(10295.4-15849.0)	3.9(3.2–4.7)	27604.9(22738.0-33544.3)	4.0(3.4–4.7)	-0.1(-0.2,-0.0)
Middle SDI	41316.8(37438.9-46864.0)	3.3(3.0-3.8)	137684.0(121796.8-154465.2)	5.1(4.5–5.7)	1.4(1.3,1.5)
Andean Latin America	1840.9(1625.8-2154.9)	7.5(6.6–8.8)	12332.3(9806.5-15421.2)	20.2(16.1–25.3)	3.3(3.2,3.5)
Australasia	3184.4(3005.0-3363.3)	13.9(13.1–14.7)	8213.9(7193.0-9252.4)	16.6(14.7–18.5)	0.3(-0.1,0.6)
Caribbean	2119.0(1980.9-2286.8)	7.3(6.8–7.8)	3845.4(3397.3–4351.0)	7.4(6.5–8.3)	0.1(-0.0,0.3)
Central Asia	1580.2(1472.1-1706.1)	2.7(2.5–2.9)	2320.2(2045.1-2623.5)	2.5(2.2–2.9)	-0.3(-0.5,-0.0)
Central Europe	6056.3(5826.2-6345.6)	4.2(4.1–4.4)	14579.7(13385.2-15838.2)	7.5(6.9–8.2)	1.9(1.6,2.2)
Central Latin America	4042.9(3938.1-4157.7)	3.8(3.7–3.9)	15416.5(13748.8-17010.3)	6.1(5.4–6.7)	1.3(1.1,1.4)
Central Sub-Saharan Africa	931.9(676.4-1286.8)	2.9(2.1–4.1)	2328.1(1690.8-3142.3)	3.2(2.3–4.4)	0.2(0.0,0.4)
East Asia	32517.4(28165.9-39418.4)	3.3(2.9-4.0)	114586.9(90509.9-139097.6)	5.5(4.4–6.7)	1.8(1.6,2.1)
Eastern Europe	11531.4(11175.7-12000.4)	4.5(4.3–4.6)	24488.4(22698.1-26351.8)	7.9(7.3–8.5)	1.9(1.5,2.3)
Eastern Sub-Saharan Africa	6947.1(5484.7-8366.2)	6.1(4.8–7.2)	14567.3(11598.3-18628.5)	6.1(5.0-7.6)	-0.2(-0.3,-0.1)
High-income Asia Pacific	12447.1(11655.2-13239.4)	6.3(5.9–6.7)	41407.2(35512.0-47167.5)	9.6(8.5–10.8)	1.3(1.1,1.6)
High-income North America	64908.5(61881.2-66927.1)	19.3(18.4–19.8)	97865.4(89280.9-103519.6)	15.9(14.7–16.8)	-1.2(-1.5,-0.9)
North Africa and Middle East	8156.1(6886.0-10107.4)	3.7(3.1–4.6)	27800.8(23911.9-34337.5)	5.4(4.6–6.6)	1.3(1.3,1.4)
Oceania	97.1(75.0-130.8)	2.2(1.7–2.9)	271.6(201.4–353.0)	2.6(2.0-3.3)	0.6(0.5,0.6)
South Asia	20483.3(17352.4-24074.8)	2.8(2.3–3.3)	54303.7(48058.7-65016.6)	3.4(3.0-4.1)	0.5(0.4,0.6)
Southeast Asia	8862.1(7595.4-11266.5)	2.8(2.4–3.6)	24885.3(21291.0-33269.3)	3.6(3.1–4.9)	0.7(0.6,0.7)
Southern Latin America	2758.3(2615.6-2904.6)	5.8(5.5–6.2)	5631.8(5103.5-6088.4)	6.8(6.2–7.4)	0.5(0.1,0.8)
Southern Sub-Saharan Africa	1345.0(1186.4-1535.5)	3.8(3.3–4.3)	4247.4(3372.2-4830.6)	6.1(4.9-7.0)	1.8(1.5,2.2)
Tropical Latin America	4577.2(4423.4-4732.3)	4.2(4.0-4.4)	13235.3(12414.7-13939.9)	5.2(4.9–5.5)	0.4(0.2,0.7)
Western Europe	57413.8(54923.6-59484.0)	11.2(10.7–11.5)	112416.6(102315.1-121619.4)	14.3(13.3–15.2)	0.5(0.2,0.8)
Western Sub-Saharan Africa	3867.8(3048.9-4663.9)	2.8(2.2–3.2)	9810.3(6993.6-12205.0)	3.3(2.4–3.9)	0.4(0.4,0.5)

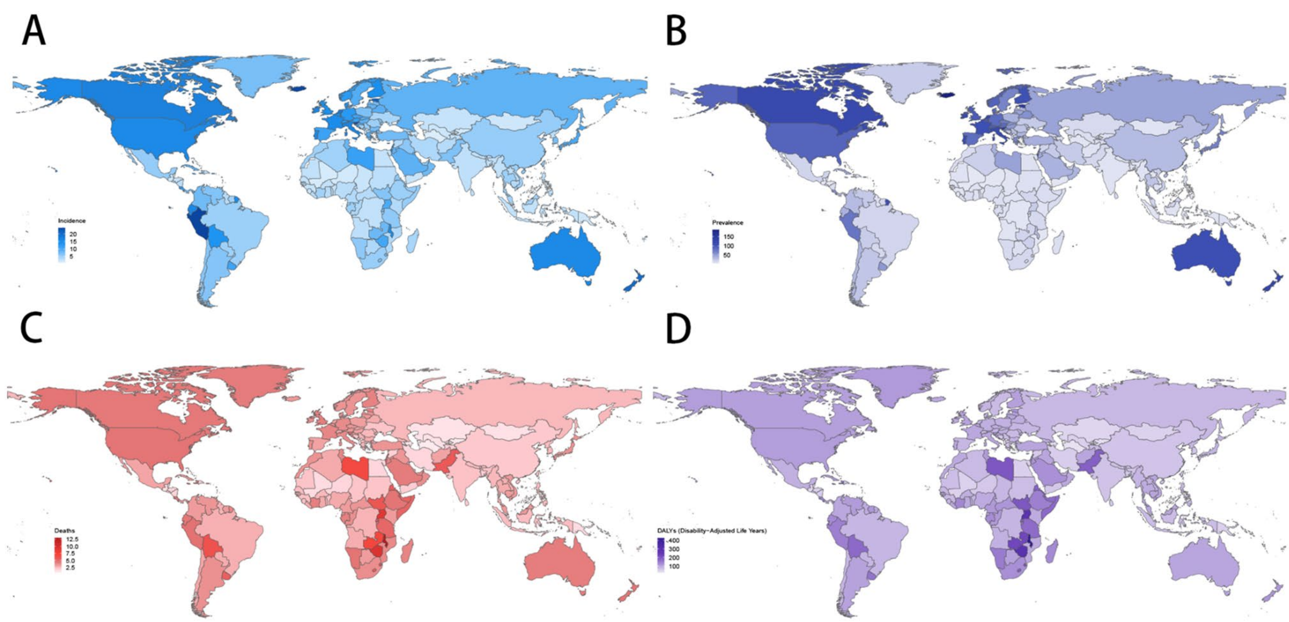

Fig. 1 The age-standardized incidence rate (**A**), age-standardized prevalence rate (**B**), age-standardized mortality rate (**C**), and age-standardized DALY rate (**D**) of non-Hodgkin lymphoma in 204 countries and territories in 2021

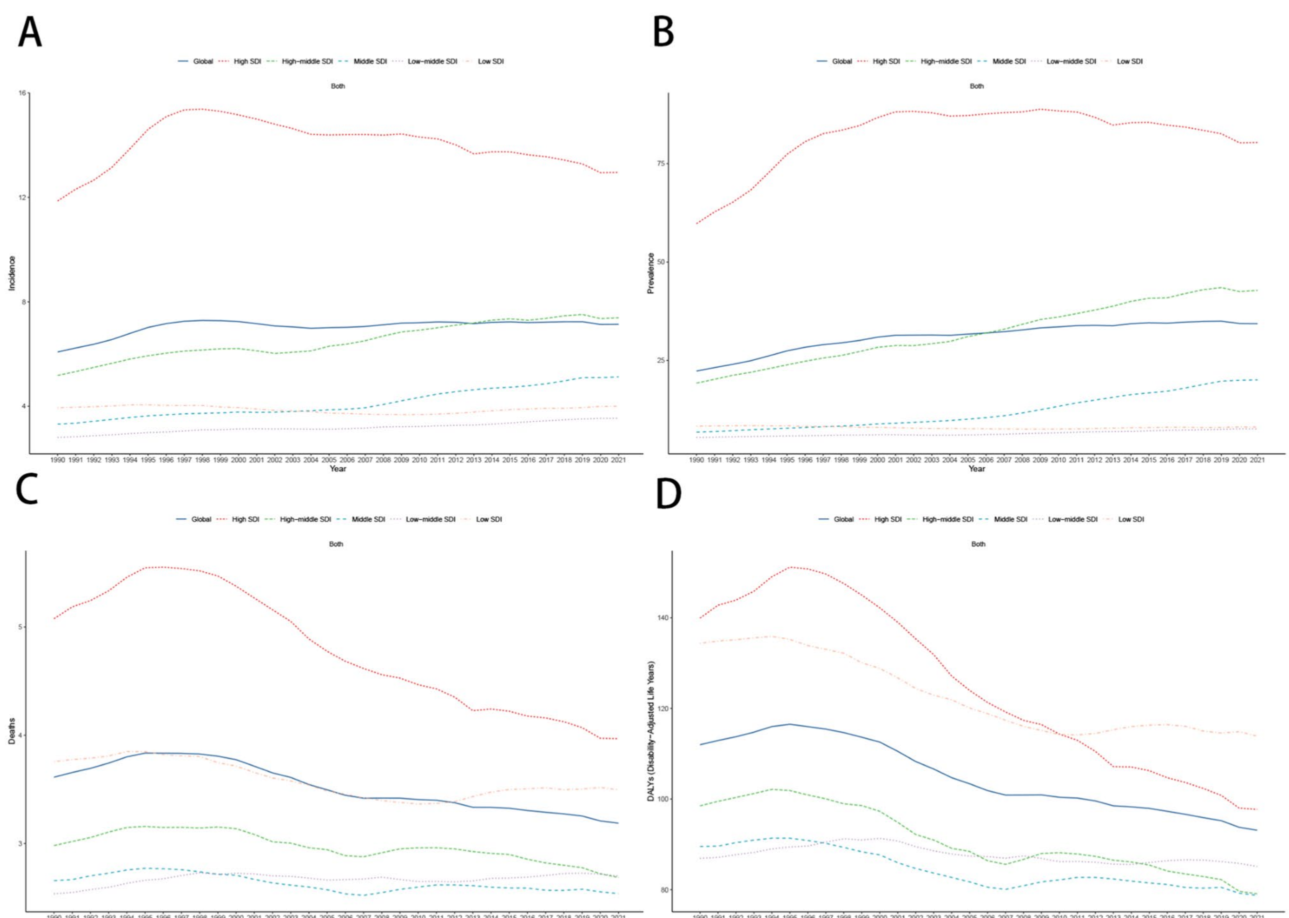

Fig. 2 Trends in the age-standardized incidence rate (**A**), age-standardized prevalence rate (**B**), age-standardized mortality rate (**C**) and age-standardized DALY rate (**D**) of NHL across the five SDI regions from to 1990–2021

Table 2 Global prevalence of NHL in 1990 and 2021 and the corresponding average annual percent change (AAPC)

location	1990 (95% UI)		2021 (95% UI)		AAPC
	Number	ASPR	Number	ASPR	
Global	1035772.9(973877.3-1097061.4)	22.3(21.0-23.5)	2919051.7(2693927.0-3150864.8)	34.3(31.6–37.0)	1.2(1.0,1.5)
High-middle SDI	203418.1(189975.6-216417.8)	19.2(18.0-20.4)	750834.1(668155.7-840472.6)	42.8(38.3–47.5)	2.6(2.5,2.8)
High SDI	607650.0(577779.6-637275.6)	59.8(57.1–62.4)	1393376.2(1302596.6-1479248.3)	80.4(75.9–84.6)	0.7(0.3,1.0)
Low-middle SDI	64503.1(51075.5-78525.5)	5.4(4.6–6.5)	141916.7(121813.8-175683.8)	7.6(6.5–9.4)	1.1(1.0,1.1)
Low SDI	46767.4(34490.8-58758.8)	8.3(6.3–10.2)	88515.5(67282.3-110917.5)	8.1(6.4–9.9)	-0.2(-0.3,-0.1)
Middle SDI	112580.1(100089.2-128205.6)	6.8(6.1–7.6)	541931.7(460802.0-622806.1)	20.1(17.2–23.0)	3.9(3.6,4.1)
Andean Latin America	4078.7(3586.4-4841.2)	12.1(10.7–14.2)	36311.6(27924.8-46255.0)	55.8(42.8–71.1)	5.4(5.2,5.6)
Australasia	16981.3(15918.6-18151.6)	75.3(70.8–80.2)	51168.9(44754.0-58633.2)	110.7(97.6-125.4)	1.0(0.5,1.5)
Caribbean	6829.7(6038.9-7611.8)	20.3(18.2–22.5)	14853.9(12982.6-17080.4)	29.2(25.5–33.7)	1.4(1.2,1.6)
Central Asia	6382.1(5699.4–7194.0)	8.7(7.9–9.8)	9888.2(8560.5-11338.5)	10.1(8.8–11.6)	0.4(-0.0,0.7)
Central Europe	18489.2(16949.0-19961.2)	13.9(12.8–14.9)	72045.0(65257.8-79680.8)	41.9(38.1–45.8)	3.7(3.3,4.2)
Central Latin America	11865.6(11117.9-12661.2)	7.7(7.2–8.1)	49936.3(43224.3-56779.5)	19.2(16.6–21.8)	3.1(2.9,3.2)
Central Sub-Saharan Africa	2969.0(1884.9-4211.6)	5.5(4.0-7.8)	6105.0(4360.9-8185.7)	5.4(3.9–7.4)	-0.0(-0.2,0.1)
East Asia	84945.1(73480.1-100238.2)	7.3(6.4–8.7)	630411.3(493370.3-780476.3)	31.0(24.5–37.9)	5.3(5.1,5.6)
Eastern Europe	41114.1(38092.7-44158.1)	17.7(16.5–18.9)	115138.1(105171.3-125644.0)	41.0(37.8–44.2)	2.7(2.1,3.3)
Eastern Sub-Saharan Africa	25448.4(18845.4-32440.6)	12.3(9.5–15.0)	47227.3(35308.9-63013.5)	11.8(9.2–15.3)	-0.2(-0.3,-0.1)
High-income Asia Pacific	64029.2(59380.3-68808.5)	32.1(29.9–34.4)	230423.2(200467.2-262121.1)	62.2(55.2–69.6)	2.1(1.7,2.6)
High-income North America	327616.2(312256.3-343640.4)	102.0(97.5-106.4)	526320.3(488637.4-559544.3)	92.1(86.5–97.3)	-0.9(-1.2,-0.5)
North Africa and Middle East	27067.2(22067.8-33467.3)	8.1(6.7–10.0)	129713.2(111751.4-157972.0)	21.9(18.8–26.4)	3.6(3.4,3.7)
Oceania	356.7(262.5–480.0)	5.2(3.9–6.9)	1035.3(750.9-1379.7)	7.1(5.2–9.2)	1.0(0.9,1.1)
South Asia	56825.9(44020.9-68984.8)	5.1(4.2–6.1)	131034.7(112639.1-156415.6)	7.3(6.3–8.7)	1.1(0.9,1.2)
Southeast Asia	23370.5(19119.7-30348.9)	5.2(4.4–6.7)	78277.0(65069.4-103792.6)	10.9(9.1–14.4)	2.3(2.2,2.4)
Southern Latin America	6534.1(5964.5-7159.3)	13.4(12.2–14.7)	21905.1(19193.6-24313.0)	28.4(25.1–31.5)	2.7(2.2,3.1)
Southern Sub-Saharan Africa	3573.8(3078.7-4279.6)	7.5(6.5–8.8)	11340.1(8637.7-13308.7)	13.9(10.6–16.2)	2.3(1.9,2.6)
Tropical Latin America	11624.3(10805.9-12456.5)	8.1(7.6–8.6)	36974.9(33632.2-41012.0)	15.0(13.6–16.5)	1.9(1.7,2.1)
Western Europe	279035.5(261914.6-295617.0)	59.8(56.5–63.0)	679817.1(628727.1-737089.1)	97.2(91.5-103.8)	1.4(0.9,1.8)
Western Sub-Saharan Africa	16636.2(12289.7-21238.3)	7.0(5.3–8.6)	39125.3(25728.7-52702.7)	7.6(5.2–9.7)	0.3(0.1,0.4)

Global, regional and National NHL death and age-standardized mortality rate in 1990, and 2021

As shown in Tables 3, 146 and 657 new deaths related to NHL were reported worldwide in 1990, and the age-standardized mortality rate (ASMR) was 3.6 cases per 100,000 people. The number of cases of new deaths related to NHL worldwide by 2021 was 267,061, and the ASMR was 3.2 cases per 100,000 people, the global AAPC for ASMR was -0.6 (-0.7,-0.5), with the largest decrease in ASMR recorded in High-income North America (AAPC: -1.8 (-2.0,-1.6)). Unlike the incidence and prevalence rates, the difference between the national and regional death rates is relatively small. Figure 1-C highlights regional differences in ASMR, with Eastern Sub-Saharan Africa having the highest death rate (ASMR = 5.4) and Central Asia having the lowest death rate (ASMR = 1.4) in 2021. Figure 2-C further illustrates the decreasing trend of NHL ASMR from 1990 to 2021 in high-SDI regions, whereas low-SDI regions show a more modest increase.

Global, regional and National NHL DALY and age-standardized DALY rate in 1990, and 2021

As shown in Table 4, the number of DALYs of global NHL in 1990 was 5,199,945, and the age-standardized DALY rate (ASDR) was 112.0 cases per 100,000 people. By 2021, the global number of DALYs was 7,766,063, and the ASDR was 93.1 cases per 100,000 people, the global AAPC for ASDR was -0.8 (-0.8,-0.7), with the largest decrease in ASDR recorded in Australasia (AAPC: (-1.9 (-2.0,-1.7)). Figure 1-D highlights the regional differences in ASDR, with Eastern Sub-Saharan Africa having the highest DALY (ASDR = 171.6) and Central Asia having the lowest DALY (ASDR = 51.9) in 2021. Figure 2-D further illustrates that the ASDR of NHL in the five SDI regions showed a downward trend from 1990 to 2021.

NHL region and sex distribution

As depicted in Fig. 3, discernible sex disparities were evident in ASIR, ASPR, ASMR, and ASDR of NHL across different regions. Specifically, in 2021, age-standardized metrics of NHL consistently demonstrated a notably greater burden among men than women in various regions of the world, with Oceania being an exception to this general trend.

NHL age and sex distribution

In 2021, a clear pattern emerged regarding age-related trends in ASIR, ASPR, ASMR, and ASDR of NHL. As

Table 3 Global mortality of NHL in 1990 and 2021 and the corresponding average annual percent change (AAPC)

Location	1990 (95% UI)		2021 (95% UI)		AAPC
	Number	ASMR	Number	ASMR	
Global	146657.4(136931.0-160542.1)	3.6(3.4–3.9)	267061.2(246094.7-288695.7)	3.2(2.9–3.4)	-0.6(-0.7,-0.5)
High-middle SDI	29529.5(27755.8-32223.9)	3.0(2.8–3.3)	50748.5(45777.5-55849.6)	2.7(2.4–2.9)	-0.4(-0.5,-0.3)
High SDI	55531.1(52796.4-57050.9)	5.1(4.8–5.2)	86990.2(77436.2-92539.9)	4.0(3.6–4.2)	-1.1(-1.3,-1.0)
Low-middle SDI	18699.4(16024.1-22494.6)	2.5(2.2–3.1)	40429.6(35952.0-50174.5)	2.7(2.4–3.4)	0.1(0.0,0.2)
Low SDI	11652.0(9244.2-14094.1)	3.8(3.0-4.5)	21895.9(18268.4-26464.8)	3.5(3.0-4.1)	-0.4(-0.5,-0.3)
Middle SDI	31097.0(28269.1-35435.8)	2.7(2.4–3.1)	66750.4(59685.1-74461.9)	2.5(2.3–2.8)	-0.2(-0.3,-0.2)
Andean Latin America	990.3(881.9-1153.4)	4.2(3.7–4.9)	2921.2(2378.1-3564.2)	4.9(4.0–6.0)	0.5(0.3,0.7)
Australasia	1457.1(1386.0-1526.2)	6.2(5.9–6.5)	2452.1(2172.1-2674.2)	4.4(3.9–4.7)	-1.5(-1.7,-1.4)
Caribbean	1282.5(1189.4-1402.8)	4.5(4.2–4.9)	1933.9(1699.6-2199.8)	3.7(3.2–4.2)	-0.5(-0.7,-0.4)
Central Asia	997.0(932.8-1068.2)	1.8(1.7–1.9)	1215.8(1062.8-1368.6)	1.4(1.2–1.6)	-0.9(-1.1,-0.7)
Central Europe	3771.3(3648.0-3968.8)	2.6(2.5–2.8)	6403.1(5877.4-6857.7)	3.0(2.8–3.2)	0.4(0.1,0.6)
Central Latin America	2626.3(2559.2-2677.3)	2.7(2.6–2.7)	7611.8(6833.8-8469.3)	3.0(2.7–3.4)	0.2(0.1,0.3)
Central Sub-Saharan Africa	851.2(621.1-1172.8)	2.9(2.0-3.9)	1911.8(1395.2-2646.2)	2.8(2.0-4.1)	-0.1(-0.2,0.1)
East Asia	25009.8(21634.5-30510.5)	2.7(2.3–3.3)	45117.6(35916.0-54232.1)	2.2(1.7–2.6)	-0.7(-0.9,-0.5)
Eastern Europe	5322.4(5163.9-5575.7)	2.0(2.0-2.1)	8319.1(7681.1-8989.1)	2.5(2.3–2.7)	0.7(0.6,0.9)
Eastern Sub-Saharan Africa	6242.3(4895.9-7568.4)	5.9(4.7–6.9)	11636.4(9384.9-14666.2)	5.4(4.5–6.7)	-0.4(-0.5,-0.3)
High-income Asia Pacific	6880.2(6506.0-7315.6)	3.5(3.3–3.7)	17806.3(15061.5-19454.8)	3.4(3.0-3.7)	-0.2(-0.3,-0.1)
High-income North America	24823.2(23347.9-25628.5)	7.1(6.7–7.3)	31443.5(27957.5-33231.2)	4.7(4.2–4.9)	-1.8(-2.0,-1.6)
North Africa and Middle East	5971.0(4993.7-7485.6)	3.0(2.5–3.8)	13299.9(11410.2-16289.0)	2.9(2.5–3.5)	-0.1(-0.1,-0.1)
Oceania	58.9(44.8–80.5)	1.7(1.4–2.3)	153.7(114.4-203.8)	1.8(1.4–2.4)	0.3(0.2,0.3)
South Asia	17416.3(14685.0-20600.3)	2.6(2.1-3.0)	39088.6(34659.7-47289.0)	2.6(2.3–3.1)	-0.1(-0.2,-0.0)
Southeast Asia	7788.0(6647.2-9891.5)	2.6(2.3–3.4)	17810.3(15167.8-23593.9)	2.7(2.3–3.6)	-0.1(-0.1,0.0)
Southern Latin America	2016.1(1929.4-2099.5)	4.3(4.2–4.5)	3070.1(2805.1-3314.8)	3.6(3.3–3.9)	-0.6(-1.0,-0.3)
Southern Sub-Saharan Africa	1017.0(898.7-1164.6)	3.1(2.7–3.6)	2898.2(2272.6–3308.0)	4.5(3.6–5.1)	1.4(1.1,1.8)
Tropical Latin America	3022.2(2914.9-3104.4)	2.9(2.8-3.0)	7046.4(6593.4-7340.3)	2.8(2.6–2.9)	-0.4(-0.6,-0.1)
Western Europe	25709.9(24493.2-26503.5)	4.5(4.3–4.7)	37383.5(33046.3-40074.0)	3.8(3.4-4.0)	-0.9(-1.1,-0.7)
Western Sub-Saharan Africa	3404.2(2693.4-4093.6)	2.6(2.1-3.0)	7537.9(5506.6-9139.3)	2.8(2.1–3.3)	0.2(0.1,0.2)

shown in Fig. 4, there was a steady increase in these metrics with advancing age. Temporal trend analysis by age group revealed prominent clustering of NHL cases, ASPR, ASMR, and ASDR within the 60–80 age bracket. Notably, the 70–75 age group bears the heaviest burden, contributing the largest proportion of ASIR, ASPR, and ASMR. Conversely, the 65–70 age group was the most significant contributor to the overall ASDR count. Furthermore, age-specific analysis in 2021 revealed that males within the age ranges of 5–14 years and 30–79 years presented significantly higher ASIR, ASMR, and ASDR of NHL than their female counterparts, with statistical significance observed across all comparisons ($P < 0.05$). Conversely, in the remaining age groups, no notable differences were detected between the sexes in these metrics ($P > 0.05$). Similarly, the ASPR of NHL among males aged 5–79 years was significantly higher than that among females in the corresponding age range ($P < 0.05$), whereas no significant sex disparity was detected in the other age groups ($P > 0.05$).

Relationship between the ASR and SDI

In 2021, across 204 countries and regions, robust positive correlations were observed between the SDI and the ASIR ($r = 0.6678$, $P < 0.01$), ASPR ($r = 0.8432$, $P < 0.01$), and ASMR ($r = 0.1657$, $P < 0.01$) of NHL. However, the ASDR of NHL was not significantly correlated with SDI ($r = 0.0089$, $P > 0.5$) (Fig. 5A-D). Moreover, from 1990 to 2021, a strong positive correlation was observed between the SDI and the ASIR ($r = 0.6982$, $P < 0.01$), ASPR ($r = 0.8561$, $P < 0.01$), and ASMR ($r = 0.3096$, $P < 0.01$) of NHL. In contrast, the ASDR of NHL demonstrated no discernible correlation with the SDI ($r = 0.0479$, $P > 0.5$). Notably, within the SDI range below 0.4, there was a gradual decrease in ASIR, ASPR, and ASMR of NHL as the SDI increased. When the SDI was less than 0.4, NHL ASIR, ASPR, and ASMR gradually decreased with increasing SDI. When the SDI is at 0.4–0.6, ASIR, ASPR, and ASMR gradually increased with increasing SDI. However, when the SDI exceeded 0.6, the ASIR, ASPR, and ASMR of NHL sharply increased as the SDI continued to increase, as illustrated in Fig. 6A-D.

Risk factors for the age-standardized mortality rate and age-standardized DALY rate

Globally, from 1990 to 2021, the primary risk factor contributing to ASMR and ASDR associated with NHL is high body mass index (BMI). Globally, the ASMR

Table 4 Global dalys of NHL in 1990 and 2021 and the corresponding average annual percent change (AAPC)

Location	1990 (95% UI)		2021 (95% UI)		AAPC
	Number	ASDR	Number	ASDR	
Global	5199945.1(4797149.9-5770128.8)	112.0(104.3-123.5)	7766063.2(7130941.8-8486078.4)	93.1(85.4–102.0)	-0.8(-0.8,-0.7)
High-middle SDI	1023032.2(959072.1-1123822.9)	98.5(92.5-108.3)	1391376.4(1247763.4-1536478.4)	79.1(71.0–87.0)	-0.8(-0.9,-0.7)
High SDI	1456819.8(1409621.6-1494870.5)	139.9(135.6-143.6)	1828277.6(1680865.1-1932343.0)	97.7(91.1-102.7)	-1.5(-1.7,-1.4)
Low-middle SDI	837865.8(709519.1-1021810.5)	86.9(74.6-104.3)	1445133.0(1265767.5-1794764.3)	85.1(74.9-105.8)	-0.2(-0.2,-0.1)
Low SDI	593579.6(453708.1-739122.2)	134.4(106.7-162.1)	983444.8(792137.9-1218266.6)	113.9(95.0-138.0)	-0.7(-0.8,-0.6)
Middle SDI	1283494.6(1155806.1-1475475.2)	89.5(80.6-102.1)	2110661.5(1869847.4-2351317.2)	78.7(69.8–87.5)	-0.5(-0.6,-0.4)
Andean Latin America	39961.7(35519.0-46466.3)	135.3(120.7-157.8)	89924.6(72998.8-109357.5)	144.0(117.0-175.3)	0.2(0.0,0.3)
Australasia	37996.2(36450.5-39655.7)	166.5(159.5-173.7)	51919.9(46926.5-55951.4)	105.0(96.0-112.7)	-1.9(-2.0,-1.7)
Caribbean	50331.7(44191.2-57297.5)	159.0(142.6-178.1)	64467.6(55024.5-75815.6)	128.1(108.2-151.9)	-0.6(-0.8,-0.4)
Central Asia	46853.3(43155.8-50851.4)	73.1(68.1–78.8)	48739.1(42894.6-55140.9)	51.9(45.7–58.5)	-1.4(-1.6,-1.2)
Central Europe	117972.0(114498.2-123685.4)	84.4(82.0-88.4)	157011.7(144211.1-168013.1)	84.9(78.2–91.0)	-0.1(-0.3,0.2)
Central Latin America	109172.6(106535.4-112065.7)	86.2(84.2–88.0)	233643.1(208667.0-261431.4)	90.8(81.2-101.6)	-0.0(-0.1,0.1)
Central Sub-Saharan Africa	40973.2(29386.1-57574.0)	96.1(70.1-132.5)	80963.0(58764.0-109525.9)	89.2(65.4-123.2)	-0.2(-0.4,-0.1)
East Asia	995904.2(856728.9-1208900.3)	92.6(79.8-112.4)	1339489.4(1058542.9-1617166.4)	67.9(54.1–80.8)	-1.0(-1.3,-0.8)
Eastern Europe	191007.4(185354.9-200180.6)	76.9(74.6–80.2)	242153.1(223208.6-263284.9)	82.4(75.7–89.6)	0.1(-0.1,0.2)
Eastern Sub-Saharan Africa	322004.6(248084.1-403351.4)	203.3(159.5-246.8)	526658.4(406511.8-688285.6)	171.6(138.3-216.7)	-0.7(-0.8,-0.6)
High-income Asia Pacific	197130.9(189637.1-210070.2)	100.7(96.7-107.6)	326267.3(291026.4-352051.6)	80.3(73.4–85.4)	-0.9(-1.0,-0.8)
High-income North America	637648.5(613417.2-655594.4)	192.4(185.9-197.5)	671809.2(624429.6-706308.2)	110.5(103.7-115.8)	-2.3(-2.5,-2.1)
North Africa and Middle East	253543.8(211641.4-320840.6)	97.5(81.9-122.8)	452123.6(390163.8-566828.8)	84.1(72.7-104.3)	-0.5(-0.5,-0.4)
Oceania	2606.8(1965.1-3604.9)	54.3(41.5–74.1)	6614.4(4842.9-8772.6)	58.7(43.5–77.4)	0.4(0.3,0.4)
South Asia	767281.9(632396.7-915285.3)	85.8(72.4-101.1)	1333536.8(1178607.1-1602374.0)	79.8(70.5–96.0)	-0.4(-0.5,-0.3)
Southeast Asia	323432.1(269446.0-408957.7)	87.1(73.9-110.3)	597432.7(508450.5-786363.7)	84.4(72.0-111.5)	-0.2(-0.3,-0.2)
Southern Latin America	64462.0(61563.3-67129.5)	134.9(129.0-140.6)	81982.2(76035.4-88308.6)	101.8(94.3-109.7)	-0.9(-1.2,-0.6)
Southern Sub-Saharan Africa	43232.5(38182.2-49738.1)	107.9(95.3-123.5)	113830.9(87681.2-131805.1)	154.8(120.3-178.4)	1.5(1.1,1.9)
Tropical Latin America	119160.6(115173.8-122976.9)	96.3(93.3–99.0)	209442.8(199849.7-217921.1)	83.1(79.2–86.5)	-0.7(-0.9,-0.4)
Western Europe	651368.5(631737.9-668880.3)	127.7(124.2–131.0)	764521.3(695089.3-814932.8)	94.5(88.1-100.3)	-1.3(-1.5,-1.1)
Western Sub-Saharan Africa	187900.9(143715.6-233759.3)	98.4(78.7-117.4)	373532.3(259090.9-468521.4)	94.1(69.1-113.9)	-0.2(-0.3,-0.1)

and ASDR of NHL are gradually increasing, primarily because of the prevalence of a high BMI. The influence of high BMI on the ASMR and ASDR of NHL has progressively intensified across regions with varying levels of SDI, including those categorized as medium-high SDI, Medium SDI, Low-medium SDI, and low SDI. After 1998, a notable shift was observed in high-SDI regions, where the influence of a high BMI on ASMR and ASDR associated with NHL gradually waned (Fig. 7A-B).

Predicting the burden of disease

This study projects the ASR of NHL from 2022 to 2040, emphasizing the global trend of anticipated increases in the ASIR and ASPR. Conversely, it forecasts a global decline in ASMR and ASDR associated with NHL (Fig. 8A-D).

Discussion

Non-Hodgkin lymphoma (NHL) poses a significant threat to human health, inflicting considerable harm and imposing a heavy burden on the society. GBD research allows us to study the burden of disease and to predict and compare disease trends [15]. This represents an inaugural comparative analysis of the GBD 2021 data pertaining to NHL, offering a comprehensive global perspective on the disease burden and its associated risk factors. In this analysis, we delved into the current trends surrounding NHL, examining the incidence, prevalence, death, and DALY rates across global, regional, and national scales. Our findings provide pivotal insights into the disease burden, underlying risk factors, and epidemiological patterns of NHL, stratified by age, sex, and geographical region. Furthermore, we have undertaken projections for global ASMR and ASDR associated with NHL up to 2040, incorporating the diverse dynamics of various age groups, sexes, and countries, to offer a comprehensive outlook on the future trajectory of this disease, which can help us conduct more rational research on strategy development, disease control, and prevention.

In this study, we found that in 2021, 604,554 new cases of NHL, 2,919,051 prevalence, 267,061 death, and 7,766,063 DALYs will occur worldwide. Globally, the incidence and prevalence of NHL has exhibited a persistent increasing trend from 1990 to 2021, which is consistent with previous studies reporting an increase in the incidence and prevalence of NHL [16]. From 1990 to 2021, the global ASIR (per 100,000 people) of NHL gradually increased from 6.1 cases in 1990 to 7.1 cases in 2021.

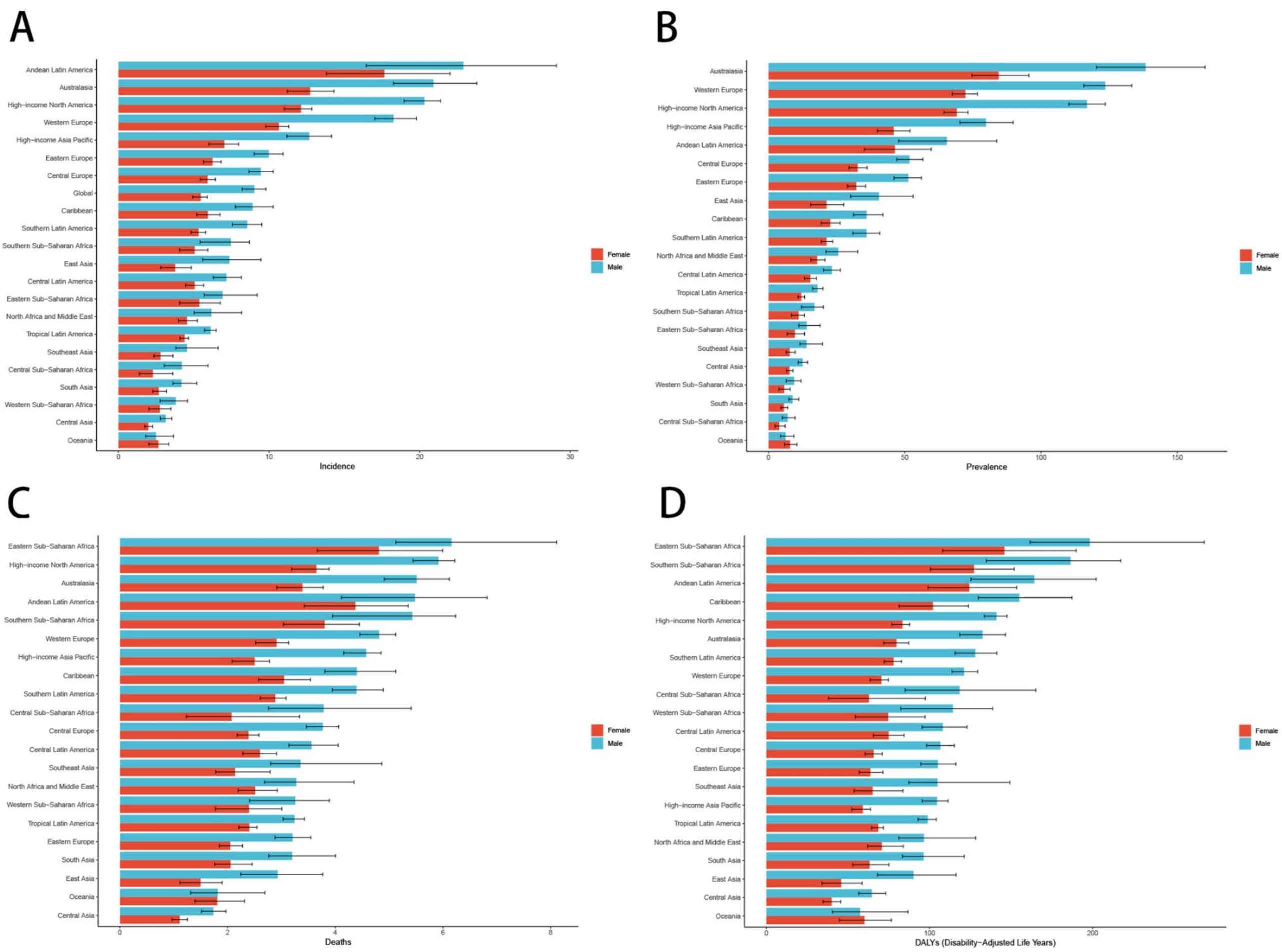

Fig. 3 The age-standardized incidence rate (**A**), age-standardized prevalence rate (**B**), age-standardized mortality rate (**C**) and age-standardized DALY rate (**D**) of NHL in 2021 were compared between men and women by region

Similarly, the ASPR of NHL has also increased steadily, from 22.3 cases in 1990 to 34.3 cases in 2021. Conversely, the ASMR and ASDR associated with NHL have gradually declined, decreasing from 3.6 deaths in 1990 to 3.2 deaths in 2021. Notably, the ASDR has also decreased marginally, from 112.0 cases in 1990 to 93.1 cases in 2021. Across all regions and nearly all age groups, the ASIR, ASPR, ASMR, and ASDR of NHL were notably higher among males than females, highlighting a pronounced sex disparity in the burden of NHL. Moreover, our study revealed that high BMI is a risk factor for NHL. Finally, our projections suggest that the ASIR and ASPR will increase further by 2040. The ASMR and ASDR will gradually decrease by 2040.

The persistent increase in NHL incidence from 1990 to 2021 may be multifactorial in nature, with several contributing factors contributing to fuel this trend. Among these are advancements in screening programs and diagnostic technologies, leading to the earlier and more accurate detection of cases. Additionally, the globalization of Western lifestyles, characterized by sedentary habits, obesity, and potential exposure to environmental factors such as radiation, has been implicated. Furthermore, factors such as advanced age, sex predisposition, and associated infections also play a significant role in increasing the incidence of NHL worldwide. The implementation of screening programs and advancements in diagnostic methodologies across numerous countries have facilitated earlier and more frequent identification of NHL cases, ultimately contributing to the observed increase in incidence rates [17]. In high-income countries, the widespread adoption of advanced diagnostic techniques such as magnetic resonance imaging (MRI) and positron emission tomography (PET) has significantly enhanced the ability to detect NHL at earlier stages, thereby contributing to increased detection rates [18]. Analogously, the progressive introduction of screening programs specifically targeting NHL in middle-income countries has resulted in a corresponding rise in incidence rates within these regions, underscoring the impact of early detection initiatives on disease incidence. Globalization of Western lifestyles, particularly in developing nations,

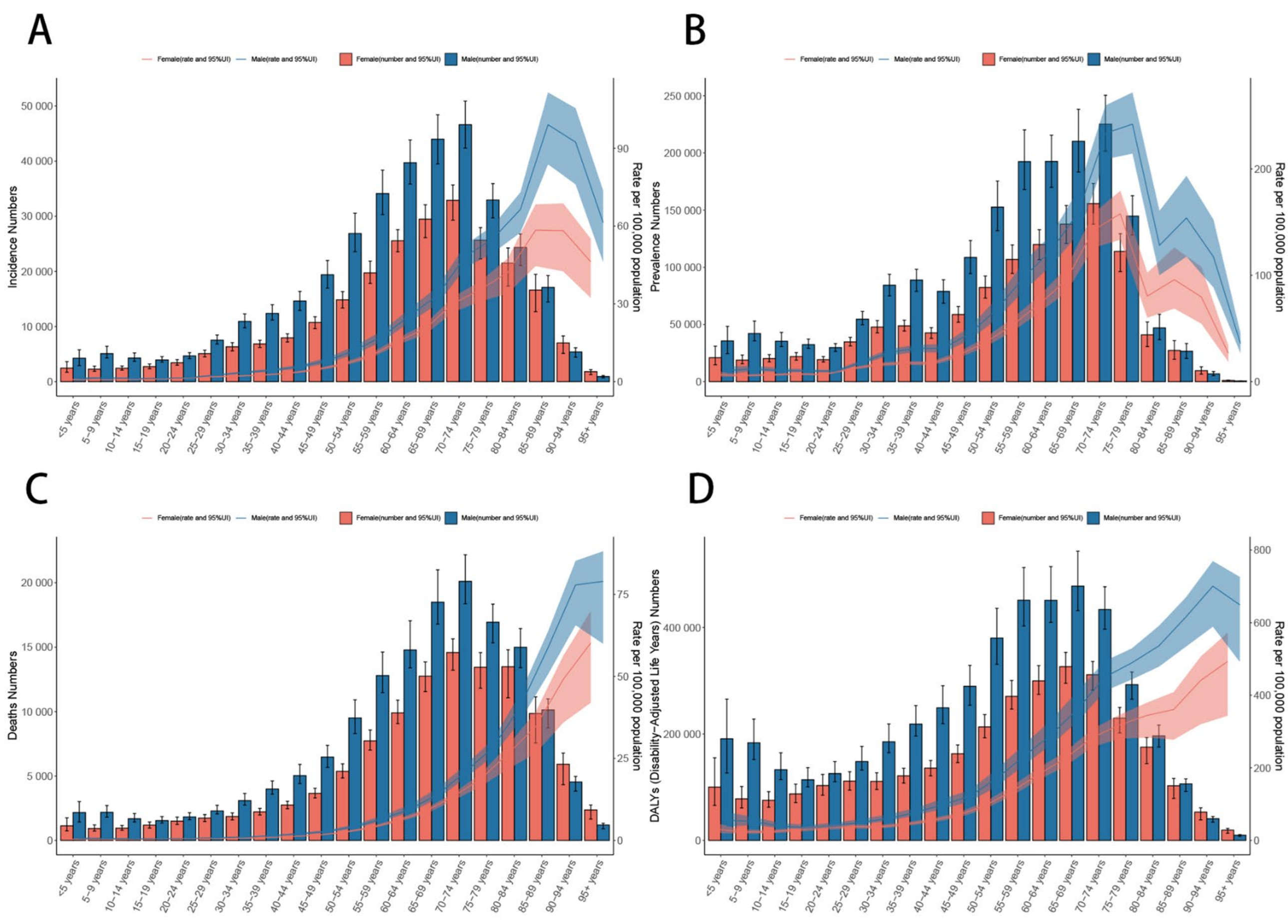

Fig. 4 The global age-standardized incidence rate (**A**), age-standardized prevalence rate (**B**), age-standardized mortality rate (**C**), and age-standardized DALY rate (**D**) of NHL per 100,000 people by age and sex in 2021

has been correlated with a surge in the incidence of NHL [19]. Decreased physical activity due to urbanization and technological advances has led to an increase in sedentary lifestyles, which are known risk factors for NHL [20]. The increasing obesity rates globally, particularly in upper-middle-income countries, constitute a pivotal contributor to the increasing incidence of NHL [21]. A comprehensive meta-analysis encompassing 16 studies revealed a robust association between being overweight and an elevated risk of developing NHL, with a particular emphasis on diffuse large B-cell lymphoma [22], and was associated with reduced patient survival [23]. Radiation exposure and environmental pollutants have emerged as potential causes of the increased incidence of NHL. Notably, studies have documented an elevated risk of NHL after radiotherapy for solid malignancies, particularly non-small cell lung cancer [24]. Exposure to a diverse array of occupational chemicals, in addition to tobacco, has been firmly established as a risk factor for various NHL [5]. Age is also a risk factor for NHL [25], and our findings revealed a marked increase in both morbidity and death rates associated with NHL among older patients.

Elderly individuals, often characterized by frailty and multiple comorbidities, experience a profound increase in death rates following NHL. The substantial growth in the elderly population (aged $\geq$65 years) observed in East Asia over the past five decades may offer a partial explanation for the upward trajectory in the incidence of NHL within these regions. These age-specific trends offer invaluable insights into the development of targeted screening and prevention strategies aimed at mitigating NHL burden in specific age cohorts. Therefore, there is an urgent need to prioritize the elucidation of NHL pathogenesis, implement preventive measures, and foster early diagnosis of NHL across all age groups. Concurrently, it is imperative to enhance the quality of life of older patients with NHL through the implementation of health promotion programs and strengthening community care services, thereby providing comprehensive support and improving their overall well-being. Remarkably, our analysis revealed a discernible trend toward younger individuals being diagnosed with NHL in recent

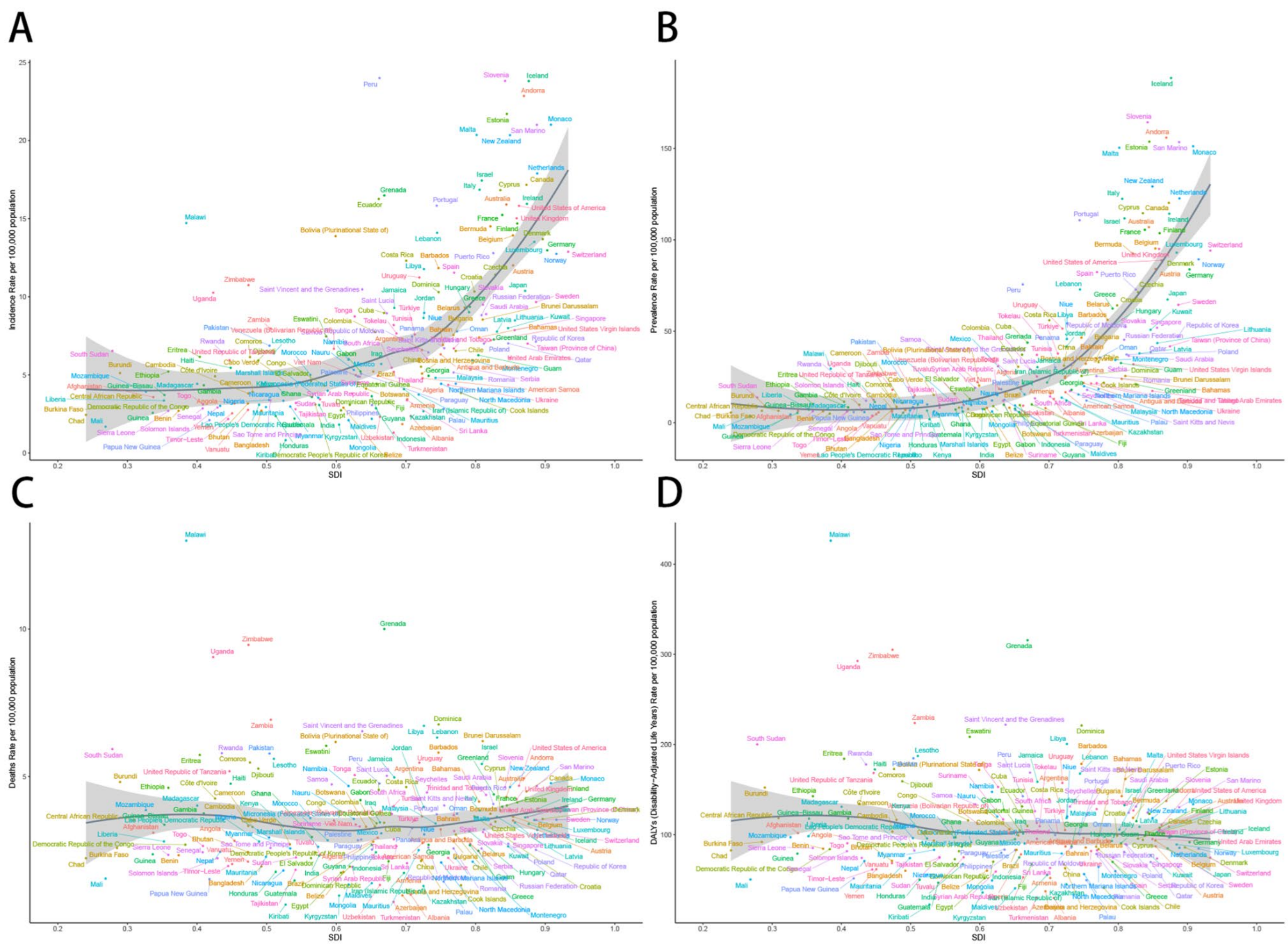

Fig. 5 2021 Association between SDI and age-standardized incidence rate (**A**), age-standardized prevalence rate (**B**), age-standardized mortality rate (**C**), and age-standardized DALY rate (**D**) of NHL in 204 countries and territories

years, accompanied by a notable surge in morbidity and death rates within this age cohort from 1990 to 2021. In line with our findings, men face a more than two-fold increased risk of developing NHL compared with women. In countries with a high human development index, men are 39% more likely to be diagnosed with NHL and have a 60% greater likelihood of succumbing to the disease than women [5]. Therefore, it is crucial to take steps to increase health and prevention awareness among men as well as to provide regular disease screening for at-risk groups. Research has consistently demonstrated that individuals infected with HIV have a significantly higher incidence of NHL than the general population [26]. According to a comprehensive study, approximately 7% of all NHL cases can be attributed to HIV. Furthermore, the global burden of HIV-related NHL incidence experienced a stark increase from 1990 to 2019, with Eastern Europe and Central Asian countries experiencing the most pronounced increasing trend during this period [27]. A meta-analysis of prospective studies conducted in Europe revealed a striking disparity in the NHL incidence among HIV-infected individuals. Specifically, the incidence rate among untreated patients was 463 cases per 100,000 person-years, whereas that among patients receiving treatment was 205 cases per 100,000 person-years. Notably, these rates are 50–100 times higher than the average risk observed in the general population [28]. The emergence and increased prevalence of HIV infection is projected to contribute to a further increase in NHL incidence. The incidence of NHL continues to increase in countries with a high prevalence of NHL continues to rise. These findings highlight the importance of implementing targeted prevention and control policies in such regions, particularly those with limited health services, to mitigate the burden of this disease. Burkitt lymphoma is strongly epidemiologically linked with Epstein-Barr virus (EBV) infection, particularly in endemic regions [29]. EBV infection increases the likelihood of MYC translocation, a process in which the MYC oncogene on chromosome 8 is repositioned to the immunoglobulin locus located on chromosome 14 [30], this translocation results in the constitutive activation of oncogenes, contributing to the

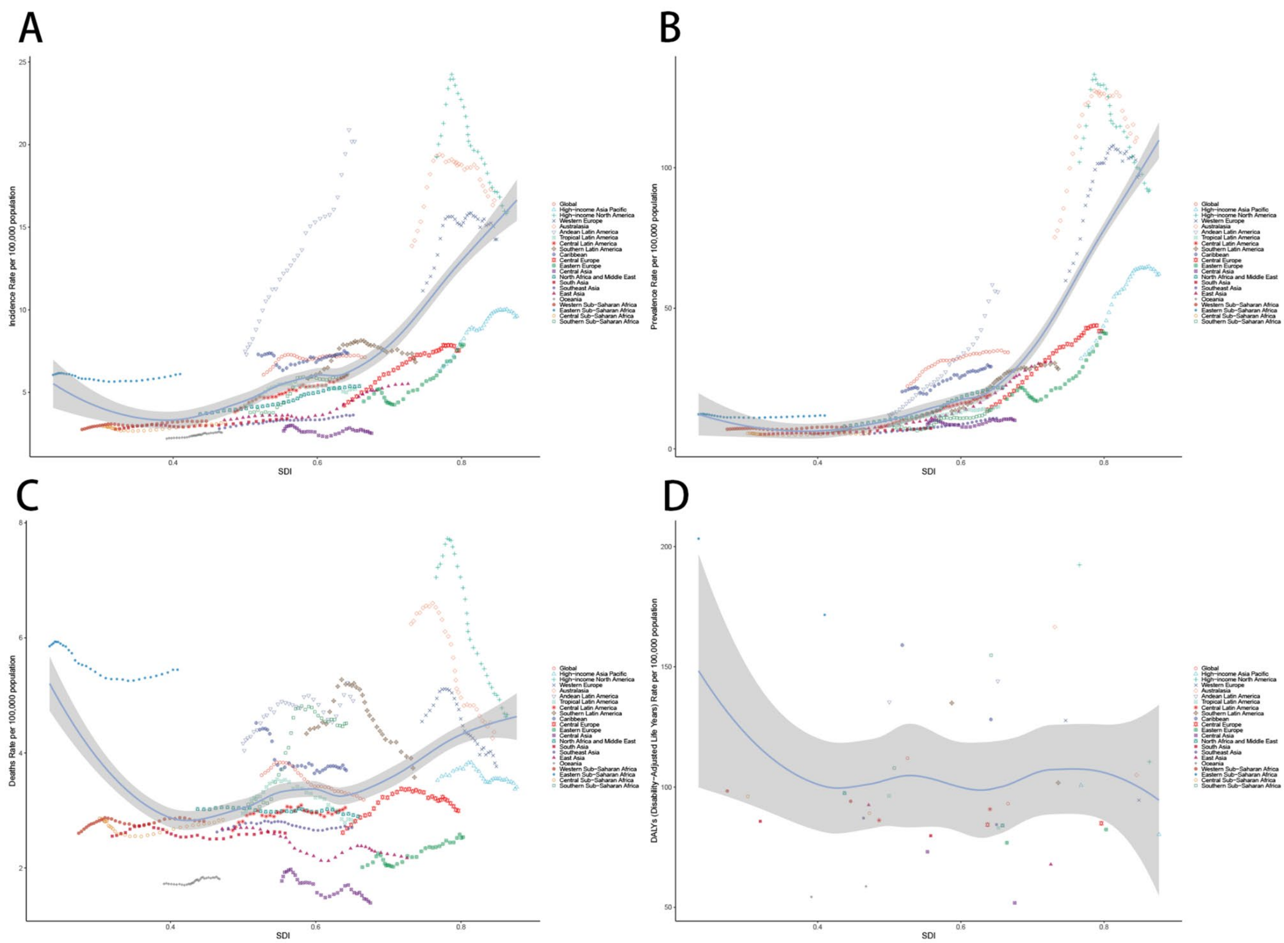

Fig. 6 Associations between SDI and the age-standardized incidence rate (**A**), age-standardized prevalence rate (**B**), age-standardized mortality rate (**C**), and age-standardized DALY rate (**D**) of NHL from 1990 to 2021

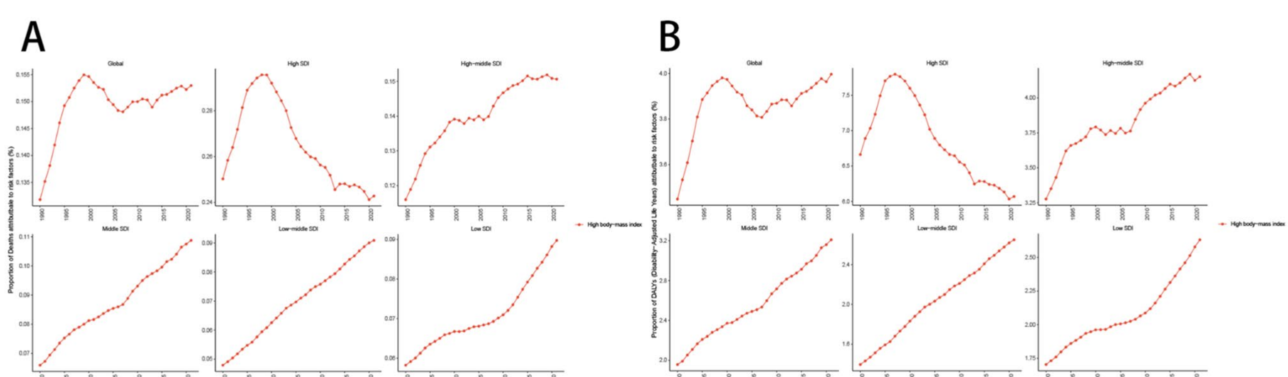

Fig. 7 Correlation between Risk factors and the age-standardized mortality rate (**A**) and age-standardized DALY rate (**B**) of NHL from 1990 to 2021

development of malignancy. In addition, our study suggests that high BMI is a risk factor for NHL. Abar L et al. study found that a high BMI was associated with the risk of NHL and was associated with a 15% increased risk of death in NHL patients [31]. A study by Teras et al. yielded similar results [32].

Globally, NHL incidence varies significantly across regions. The global incidence of NHL exhibits substantial regional variations that are intimately tied to the intricate interplay of various risk factors that collectively influence its occurrence [33]. Among the various regions worldwide, the incidence rate of NHL is notably higher in Andean Latin America, Australasia, and high-income

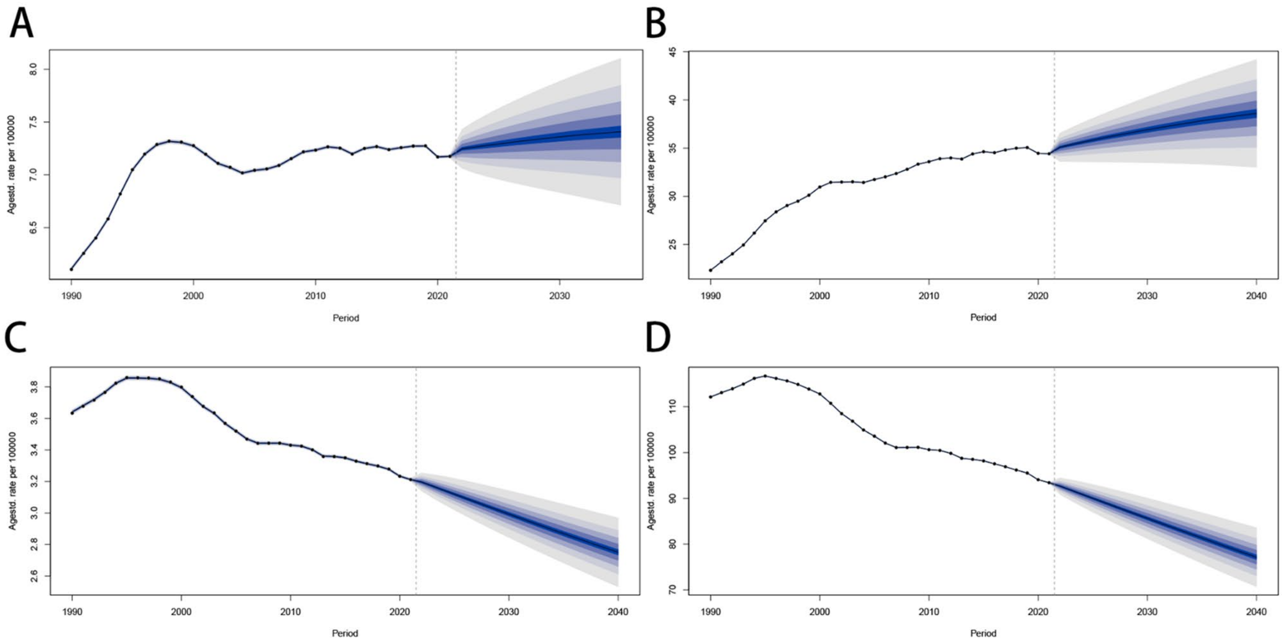

Fig. 8 The ASR of global NHL was evaluated from 1990 to 2021, and the ASR value was projected from 2022 to 2040 (**A**: age-standardized incidence rate of NHL; **B**: age-standardized prevalence rate of NHL; **C**: age-standardized mortality rate of NHL; **D**: age-standardized DALY rate of NHL)

North America, conversely, the incidence rate is relatively low in Central Asia and Oceania. Among them, Central and Eastern Europe increased significantly (AAPC: 1.9), whereas high-income North America decreased slightly (AAPC: -1.2). Endemic infections, such as HIV, EBV, and Helicobacter pylori (HP), along with environmental exposures, play pivotal roles in determining the incidence of NHL in certain regions, notably Africa, Asia, and Latin America [34]. At the same time, the high incidence rates in the Andean Latin American and Asian regions may be related to chemical exposure. Exposure to chemicals such as pesticides, insecticides, and herbicides, which are common in agricultural and industrial production in the Andean Latin American and Asian regions, may increase the risk of exposure to local populations [35, 36].

A discernible disparity exists in the ASIR of NHL between the regions with high and low SDIs. Specifically, areas characterized by a high SDI exhibited a notably higher incidence of NHL than regions with a lower SDI. One study revealed a significant positive correlation between SDI and obesity and the overweight index [37]; obesity, as an established risk factor for NHL, contributed to an increase in the incidence rate [31]. Furthermore, advancements in diagnostic techniques, including magnetic resonance imaging and positron emission tomography, have facilitated early detection of NHL, enabling prompt intervention [38]. High SDI regions tend to have better availability and accessibility of healthcare resources [39], which are essential for early detection, diagnosis, and better healthcare delivery in NHL [3]. While the incidence of NHL is relatively low in regions with a low SDI, this observation could be attributed to underreporting or underdiagnosis. These limitations may stem from a lack of screening programs, inadequate healthcare infrastructure, poor awareness, misclassification of cases, and ongoing enrollment owing to ongoing conflict or war factors.

Additionally, our research revealed that Eastern Sub-Saharan Africa, Andean Latin America, and high-income North America had notably higher death rates associated with NHL. In contrast, Central Asia, Oceania, and East Asia had lower mortality rates. The phenomenon of high NHL deaths persisted across both the developed and underdeveloped regions, which may be attributed to the convergence of several factors. These include the so-called westernization of lifestyles, diverse pathological subtypes of lymphoma, and the relatively prevalent occurrence of aggressive forms of NHL in both regions. On the one hand, the heightened deaths rate observed in low-income countries can be attributed to the prevalence of aggressive forms of NHL. A study investigating the correlation between HIV infection and NHL revealed that patients infected with HIV are more prone to develop aggressive forms of NHL [40]. Typically, the prognosis for aggressive NHL is worse [41], suggesting that in low-income countries, the elevated prevalence of HIV infection may contribute to an epidemic of aggressive NHL, ultimately leading to increased death rates. However, elevated NHL death rates may stem from disparities in healthcare resources in low-income countries, including access to early diagnosis, treatment options, and supportive care. Previous studies have underscored the constraints faced by health services in low-income countries, particularly in terms of geographic accessibility and the availability of healthcare services [42]. These limitations often result in NHL patients being unable to receive timely diagnosis and treatment, causing delays in diagnosis owing to inadequate access to medical care, which can significantly affect their prognosis. Furthermore, another study revealed that patients with NHL who experience delays in diagnosis are at risk of developing more advanced stages of the disease, subsequently increasing death rates owing to potential drug toxicity during subsequent treatment protocols [43]. Moreover, our study revealed a correlation between increased death and DALY rates in patients with NHL with increasing age. This may be attributed to the heightened risk of treatment failure among older patients who undergo attenuated-dose chemotherapy owing to comorbidities and a higher incidence of treatment-related complications [44]. Despite the emergence of novel targeted therapies that offer alternative treatment options for elderly NHL patients, enhancing treatment efficacy remains a pivotal clinical challenge. Consequently, there is a pressing need to develop innovative therapeutics and treatment strategies to significantly improve the outcomes of elderly NHL patients.

We also found that the global ASMR of NHL decreased between 1990 and 2021 from a global perspective (AAPC: -0.6 (-0.7,-0.5)). Similarly, the global ASDR of NHL decreased (AAPC: -0.8 (-0.8,-0.7)). This may be related to the advanced healthcare systems, advancements in diagnostic techniques and treatment options, and effective cancer control strategies in these regions. For example, innovative therapeutic approaches, such as stem cell transplantation, targeted medications, and immune checkpoint inhibitors, offer promising new avenues for treating patients with refractory or recurrent NHL, providing alternative treatment options [45–47]. With the advancement of novel treatment strategies and the development of effective palliative care medications, the survival prospects of patients with NHL have significantly improved, enabling them to enjoy extended lifespans [48]. Furthermore, patients diagnosed with B-cell lymphoma exhibit notably higher 5-year survival rates than those diagnosed with T-cell lymphoma. This disparity could stem from the remarkable efficacy of rituximab and anti-CD20 monoclonal antibodies in the treatment of B-cell lymphoma [49]. Additionally, advancements in diagnostic techniques, including high-resolution computed tomography (CT), magnetic resonance imaging (MRI), and flow cytometry [50, 51] as well as more precise multigene testing, are likely to play a pivotal role in enhancing the accuracy and timeliness of lymphoma diagnoses. Nevertheless, the persistent and escalating death rate in regions with a low SDI underscores the pressing necessity of enhancing access to high-quality healthcare services and comprehensive cancer control programs in these areas to address this health disparity effectively.

Our future projections indicate that while the global ASIR of NHL is anticipated to remain relatively constant at approximately 8.4 cases per 100,000 people by 2040, the absolute number of new cases will continue to increase. Concurrently, we anticipate a gradual decrease in the global ASMR of NHL, with a projected 3.0 deaths by 2040. Furthermore, the global ASDR for NHL is expected to reach 84.8, underscoring the ongoing burden of this disease, despite potential improvements in death rates. This projection underscores the persistent challenges posed by NHL and highlights the crucial need for sustained efforts toward prevention, early detection, and improved treatment strategies. The increasing absolute number of new cases underscores the urgency of these endeavors, whereas the projected gradual decline in ASMR underscores the importance of ongoing research and advancements in care. Although the global projections of the disease burden of NHL are relatively optimistic, it is important to recognize that the disease burden remains significant in some regions. Regional economic disparities, uneven access to healthcare, increasing burden of environmental and lifestyle factors, and sensitivity to historical data assumptions are important factors that cannot be ignored when using the BAPC model for forecasting. This requires us to continuously collect and analyze relevant data to gain an in-depth understanding of the actual situation in each region to more accurately grasp the development trend of NHL and other health problems and provide a scientific basis for formulating corresponding prevention and control strategies.

Limitations

While this study helps us understand trends in NHL burden and associated risk factors globally, it has several limitations. First, the precision and reliability of our findings are inherently contingent on the quality and abundance of the data utilized in the GBD study. Nevertheless, in numerous low- and middle-income countries, low-quality data can significantly contribute to substantial uncertainties in our estimates, thereby necessitating a heightened level of caution in interpreting the results. Second, there is the pervasive issue of underreporting or underdiagnosis within cancer registries, particularly in resource-constrained developing nations. This could potentially lead to a significant underestimation of the global number of deaths and DALYs attributed to NHL. Importantly, the GBD data used in our analysis did not differ among the various histological subtypes or clinical stages of NHL. Instead, it provides aggregated summary statistics, which may inherently limit the representativeness and specificity of the disease burden attributed to the individual NHL subtypes. Finally, it is crucial to acknowledge that NHL is influenced by several risk factors. However, the GBD data that we used only included high BMI as a risk factor, leaving other potential contributors unexplored. This limitation may result in an incomplete analysis of the etiology of NHL, which may affect the development of effective comprehensive prevention measures for risk factors and related intervention strategies by the relevant departments.

Conclusion

In summary, our findings underscore a persistent upward trajectory in both the ASIR and ASPR of NHL globally, juxtaposed with a consistent decline in ASMR and ASDR. This dichotomy underscores the escalating global burden of NHL and emphasizes the profound disparities across various countries and regions. The persistent increase in NHL incidence in recent years can be attributed to an increase in associated risk factors and groundbreaking advancements in early detection techniques. This trend is anticipated to persist in the coming decades, fuelled by the aging global population and cumulative impact of lifestyle-related risk factors that individuals encounter throughout their lives. The decline in NHL deaths can be attributed to remarkable advancements in various treatment modalities including chemotherapy, radiotherapy, immunotherapy, and targeted therapies. These developments have significantly contributed to improvements in patient outcomes. Future research should prioritize the development of cost-effective interventions tailored to address regional risk factors and health resource disparities worldwide with the ultimate goal of mitigating the global burden of NHL. To achieve this goal, we need to overcome various challenges, such as strengthening epidemiological research, promoting rational allocation of health resources, establishing a sound cost-benefit assessment system, improving patient compliance and social support, and strengthening development and innovation. In addition, concerted efforts must be undertaken to increase the quantity and quality of data collection in low-resource environments, enabling more precise forecasting of NHL trends, and facilitating the implementation of interventions with greater efficiency and effectiveness.

Abbreviations

AAPC	Average annual percentage change
APC	Annual percentage change
ASDR	Age-standardized DALY
ASIR	Age-standardized incidence rate
ASMR	Age-standardized mortality rate
ASPR	Age-standardized prevalence rate
ASR	Age-standardized rates
BAPC	Bayesian Age-Period-Cohort
BMI	Body mass index
CI	Confidence interval
DALYs	Disability-adjusted life years
EBV	Epstein-Barr virus
GBD	Global Burden of Diseases
NHL	Non-Hodgkin lymphoma
SDI	Sociod-Demographic Index
TFR	Total fertility rate
UI	Uncertainty interval

Acknowledgements
We appreciate the work of the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2021 collaborators.

Author contributions
S.Q.W. and H.F.Z. used software to process raw data; Y.M.L. and Y.L. designed and analyzed the study; and L.N. guided the overall idea of the text. S.Q.W. and L.N. wrote and revised the manuscript accordingly. All the authors have read and approved the final manuscript.

Funding
No funding source was received for this study.

Data availability
All anonymized data were accessed and downloaded via the Global Health Data Exchange (GHDx) platform (http://ghdx.healthdata.org/gbd-results-tool).

Declarations

Ethics approval and consent to participate
All anonymized data were accessed and downloaded via the Global Health Data Exchange (GHDx) platform (http://ghdx.healthdata.org/gbd-results-tool). Ethical approval and informed consent were not required for this study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 10 September 2024 / Accepted: 18 March 2025
Published online: 31 March 2025

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