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Global, regional, and national burden of Burkitt lymphoma from 1990 to 2021 and predictions to 2030: a systematic analysis for the Global Burden of Disease Study 2021

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Dear Editor,

Burkitt lymphoma (BL) is a highly aggressive form of non-Hodgkin lymphoma that predominantly affects young males. The age-standardized incidence rates (ASIRs) of BL show significant variation, with disparities ranging from three- to five-fold across different continents [1]. This variation is most pronounced in equatorial Africa, where the incidence rates exceed 4 cases per million person-years between 10°N to 10°S latitude, making BL endemic to this region [2, 3]. Survival outcomes for BL are influenced by multiple factors, including disease stage, geographic location, ethnicity, and treatment approaches [4, 5].

Annual data from 1990 to 2021 on incident cases, prevalent cases, deaths, and disability-adjusted life years (DALYs) of BL, as well as ASIRs, age-standardized prevalence rates (ASPRs), age-standardized mortality rates (ASMRs), and age-standardized DALY rates (ASDRs), were obtained using the Global Health Data Exchange (GHDx) query tool (http://ghdx.healthdata.org/gbd-results-tool). Socioeconomic data, comprising the Socio-Demographic Index (SDI) [6] for 2021, the Universal Health Coverage Index (UHCI) [7] values for 2019, and the Human Development Index (HDI) [8] were also collected. The estimated annual percentage change (EAPC) was used to summarize changes in age-standardized rates (ASRs) over time. Joinpoint regression analysis was applied to detect shifts in trends and identify critical points of change. To explore the relationship between EAPCs and socioeconomic factors, Spearman correlation analyses were conducted. Additionally, we performed a decomposition analysis focusing on the contributions of age structure, epidemiologic changes, and population size. Finally, using the Bayesian APC (BAPC) model [9], we projected the absolute numbers, rates, and ASRs until 2030.

The global, regional, and national number of incident cases, prevalent cases, and deaths due to BL, along with their trends from 1990 to 2021, are presented in Table 1 and Supplementary Tables 1, 2. In 2021, the global incident and prevalent cases of BL were 19.07 thousand and 126.62 thousand, respectively. From 1990 to 2021, all metrics for BL exhibited an upward trend. Joinpoint regression analysis revealed significant shifts in the incidence and prevalence of BL in 1993, 2001, 2007, and 2017 (Supplementary Figure 1). High SDI quintiles displayed increasing trends in all metrics, with EAPCs ranging from 0.65 to 2.77. In contrast, low SDI quintiles showed declining trends in these metrics.

Among the 21 GBD regions, Eastern Sub-Saharan Africa exhibited the highest ASIR and ASPR of BL in 1990 (Supplementary Tables 1, 2). However, by 2021, the highest ASIR and ASPR had shifted to High-income North America, where Canada and the United States recorded rates of 0.61 and 0.72 per 100,000 population, respectively. Conversely, in 1990, Southeast Asia reported the lowest ASIR and ASPR, but by 2021, the lowest rates had moved to Central Asia (Fig. 1). During this period, Central Europe observed the most pronounced increases in both ASIR and ASPR, while Oceania experienced the sharpest rise in ASMR. Furthermore, the Eastern Sub-Saharan Africa region consistently exhibited the highest ASMR for BL in both 1990 and 2019. Initially, the regions with the lowest ASMR in 1990 included Southeast Asia, South Asia, East Asia, Oceania, and Central Asia. By 2021, however, East Asia and Central Asia had the lowest ASMR (Supplementary Fig. 2). Meanwhile, Southern Latin America consistently recorded the highest ASDR during these years, with Southern Sub-Saharan Africa showing the most significant rise in ASDR over time (Supplementary Fig. 3).

The number of incident cases, prevalent cases, and deaths of BL was consistently higher in males than in females (Supplementary Figs. 4, 5). Globally, the trends in all metrics exhibited greater increases in males compared to females (Supplementary Fig. 6). In 1990, the ASIR of BL in males was 2.125 times that of females, decreasing to 2 times by 2021; conversely, the ASPR was 1.98 times higher in males than in females in 1990, increasing slightly to 2.02 times by 2021.

Males demonstrated higher ASIR and ASPR of BL in high SDI quintiles in both 1990 and 2021 (Supplementary Table 3). Conversely, while females exhibited the highest ASIR and ASPR in low SDI quintiles in 1990, by 2021, these rates had shifted to be highest in high SDI quintiles. In the middle SDI quintiles, a noticeable decline in ASDR was observed for females, with no significant changes noted for males. In the 21 GBD regions, the most significant increase trends in ASIR for both genders were observed in Central Europe. Among the 204 countries and territories, Cyprus and Albania exhibited the highest increases in ASIR for males and females, respectively (Supplementary Table 4). In 1990 and 2021, BL showed higher incidence, prevalence, mortality rates, and DALYs among the 0-14 age group (Supplementary Fig. 4). However, by 2021, the distribution of incidence and prevalence rates had expanded to include middle-aged and older populations. Despite this broader age distribution for incidence and prevalence, the highest mortality rates and DALYs continued to be concentrated in the 0-14 age group.

In 1990, the ASIR and ASPR of BL showed no correlation with SDI and HDI. However, by 2021, both rates exhibited a positive correlation (Supplementary Figs. 7, 8). The ASMR and ASDR of BL were negatively correlated with SDI and HDI. The temporal changes in ASIR, ASPR, ASMR, and ASDR of BL from 1990 to

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Table 1. The global and regional incident cases, prevalent cases, and their change trends of Burkitt lymphoma from 1990 to 2021.

Location	1990		2021		EAPC (95% CI)	1990		2021		EAPC (95% CI)
	Incident cases (95% UI)	ASR per 100,000	Incident cases (95% UI)	ASR per 100,000		Prevalent cases (95% UI)	ASR per 100,000	Prevalent cases (95% UI)	ASR per 100,000	
Global	6194.85 (4466.29 to 8140.39)	0.13 (0.09 to 0.17)	19072.93 (9650.59 to 32508.93)	0.24 (0.12 to 0.4)	2.18 (1.8 to 2.56)	43725.37 (31030.08 to 57607)	0.86 (0.63 to 1.15)	126620.21 (66345.22 to 208589.81)	1.57 (0.84 to 2.55)	2.12 (1.77 to 2.48)
High SDI	2229.01 (1605.01 to 3375.5)	0.23 (0.16 to 0.34)	8834.96 (3391.98 to 17415.62)	0.51 (0.21 to 0.94)	2.77 (2.19 to 3.36)	14503.88 (10417.28 to 21984.32)	1.49 (1.07 to 2.27)	54979.41 (21708.42 to 105737.48)	3.37 (1.42 to 6.05)	2.77 (2.19 to 3.35)
High-middle SDI	890.73 (632.95 to 1235.84)	0.09 (0.06 to 0.12)	3691.14 (1503.98 to 7343.39)	0.23 (0.1 to 0.43)	3.45 (3.08 to 3.82)	6183.59 (4351.24 to 8575.43)	0.61 (0.43 to 0.84)	23891.44 (9896.6 to 46421.55)	1.52 (0.68 to 2.75)	3.36 (3.01 to 3.71)
Low SDI	1715.44 (778.41 to 2617.33)	0.26 (0.12 to 0.4)	2861.14 (1577.26 to 3907.98)	0.22 (0.12 to 0.33)	−0.58 (−0.63 to −0.54)	12902.29 (5862.38 to 19605.64)	1.94 (0.86 to 2.92)	21538.47 (11930.83 to 29862.78)	1.64 (0.87 to 2.41)	−0.55 (−0.6 to −0.51)
Low-middle SDI	735.89 (410.76 to 1029.09)	0.05 (0.03 to 0.07)	1527.48 (1006 to 2019.25)	0.08 (0.05 to 0.11)	1.35 (1.28 to 1.42)	5536.55 (3086.3 to 7838.89)	0.39 (0.23 to 0.54)	11258.16 (7311.33 to 14807.23)	0.59 (0.38 to 0.78)	1.31 (1.24 to 1.38)
Middle SDI	618.61 (424.66 to 812.96)	0.04 (0.03 to 0.05)	2143.05 (1175.05 to 3112.73)	0.09 (0.05 to 0.13)	2.89 (2.71 to 3.07)	4562.69 (3139.33 to 6061.53)	0.27 (0.19 to 0.36)	14852.59 (8164.77 to 21300.3)	0.61 (0.34 to 0.87)	2.79 (2.62 to 2.96)
Andean Latin America	30.11 (21.01 to 48.13)	0.08 (0.05 to 0.12)	125.51 (50.27 to 215.2)	0.2 (0.08 to 0.34)	3.31 (3.18 to 3.43)	224.57 (157.27 to 359.48)	0.55 (0.39 to 0.88)	878.28 (364.94 to 1501.92)	1.39 (0.57 to 2.4)	3.14 (3.02 to 3.26)
Australasia	48.86 (33.96 to 72.1)	0.23 (0.16 to 0.34)	196.69 (70.82 to 450.09)	0.45 (0.17 to 0.97)	2.18 (1.58 to 2.78)	326.61 (225.36 to 486.99)	1.54 (1.08 to 2.3)	1259.84 (468.45 to 2829.64)	3.01 (1.19 to 6.33)	2.14 (1.53 to 2.74)
Caribbean	58.05 (35.72 to 95.9)	0.17 (0.1 to 0.28)	105.04 (62.5 to 162.52)	0.21 (0.13 to 0.32)	1.57 (1.25 to 1.89)	419.07 (258.26 to 689.02)	1.22 (0.75 to 2)	714.54 (425 to 1085.42)	1.45 (0.86 to 2.2)	1.51 (1.19 to 1.83)
Central Asia	18.75 (10.45 to 29.25)	0.03 (0.02 to 0.05)	19.46 (10.87 to 30.59)	0.02 (0.01 to 0.03)	−1.06 (−1.68 to −0.43)	135.79 (75.97 to 211.68)	0.2 (0.11 to 0.31)	138.05 (76.38 to 213.69)	0.15 (0.08 to 0.23)	−1.1 (−1.74 to −0.46)
Central Europe	76.69 (48.25 to 122.76)	0.06 (0.04 to 0.09)	317.39 (114.41 to 623.57)	0.19 (0.07 to 0.35)	4.24 (3.61 to 4.86)	516.05 (327.73 to 813.8)	0.39 (0.25 to 0.62)	2016.59 (737.17 to 3912.09)	1.3 (0.5 to 2.35)	4.22 (3.6 to 4.85)
Central Latin America	115.94 (80.69 to 175.75)	0.08 (0.05 to 0.12)	519.17 (270.77 to 835.57)	0.21 (0.11 to 0.33)	3.23 (2.89 to 3.57)	848.86 (589.16 to 1281.3)	0.55 (0.38 to 0.85)	3595.59 (1886.26 to 5743.99)	1.44 (0.75 to 2.29)	3.2 (2.86 to 3.54)
Central Sub-Saharan Africa	178.25 (69.04 to 304.39)	0.27 (0.1 to 0.44)	263.83 (117.71 to 399.8)	0.2 (0.08 to 0.31)	−1 (−1.05 to −0.94)	1336.33 (500.9 to 2240.25)	1.95 (0.74 to 3.2)	1959.09 (879.45 to 2960.3)	1.42 (0.57 to 2.18)	−1.03 (−1.08 to −0.97)
East Asia	311.47 (158.02 to 464.05)	0.03 (0.01 to 0.04)	1368.75 (625.41 to 1971.91)	0.08 (0.04 to 0.11)	3.17 (2.91 to 3.44)	2279.88 (1133.89 to 3374.23)	0.2 (0.1 to 0.3)	8942.81 (4112.02 to 12862.28)	0.53 (0.25 to 0.74)	2.86 (2.6 to 3.12)
Eastern Europe	140.83 (84.84 to 214.97)	0.06 (0.04 to 0.1)	207.39 (82.78 to 354.91)	0.09 (0.04 to 0.15)	1.88 (1.32 to 2.45)	1006.48 (604.83 to 1545.07)	0.47 (0.28 to 0.71)	1406.9 (560.55 to 2393.88)	0.65 (0.26 to 1.05)	1.84 (1.27 to 2.42)
Eastern Sub-Saharan Africa	1140.71 (490.15 to 1748.06)	0.48 (0.2 to 0.73)	1786.6 (915.77 to 2589.95)	0.39 (0.19 to 0.61)	−0.79 (−0.83 to −0.74)	8557.8 (3740.86 to 13122.11)	3.48 (1.45 to 5.3)	13395.18 (7052.66 to 19216.59)	2.82 (1.38 to 4.44)	−0.75 (−0.79 to −0.71)
High-income Asia Pacific	291.57 (132.7 to 495.15)	0.16 (0.07 to 0.26)	1490.83 (550.08 to 2870.54)	0.39 (0.15 to 0.69)	3.01 (2.45 to 3.58)	1900.6 (860.27 to 3194.87)	1.01 (0.47 to 1.7)	9014.14 (3410.29 to 16819.68)	2.56 (1.01 to 4.43)	3.04 (2.47 to 3.62)

Table 1. continued

Location	1990		2021		EAPC (95% CI)	1990		2021		EAPC (95% CI)
	Incident cases (95% UI)	ASR per 100,000	Incident cases (95% UI)	ASR per 100,000		Prevalent cases (95% UI)	ASR per 100,000	Prevalent cases (95% UI)	ASR per 100,000	
High-income North America	1198.38 (836.95 to 1784.13)	0.38 (0.27 to 0.56)	3928.15 (1698.22 to 6760.97)	0.71 (0.33 to 1.16)	2.23 (1.63 to 2.84)	7786.68 (5451 to 11597.85)	2.53 (1.77 to 3.73)	24605.84 (11052.23 to 40905.3)	4.66 (2.24 to 7.37)	2.2 (1.61 to 2.8)
North Africa and Middle East	221.13 (132.31 to 341.67)	0.06 (0.04 to 0.09)	775.07 (443.13 to 1116.63)	0.14 (0.08 to 0.2)	2.98 (2.78 to 3.18)	1648.85 (967.65 to 2513.66)	0.45 (0.27 to 0.68)	5559.29 (3198.6 to 7930.65)	0.95 (0.54 to 1.39)	2.83 (2.64 to 3.03)
Oceania	1.27 (0.71 to 2.08)	0.02 (0.01 to 0.03)	5.18 (1.95 to 9.38)	0.04 (0.02 to 0.08)	2.4 (2.17 to 2.62)	9.31 (5.12 to 15.5)	0.15 (0.09 to 0.23)	37.52 (14.28 to 67.35)	0.3 (0.12 to 0.53)	2.39 (2.16 to 2.62)
South Asia	338.31 (132.74 to 542.49)	0.03 (0.01 to 0.04)	493.06 (230.87 to 728.81)	0.03 (0.01 to 0.04)	0.12 (−0.06 to 0.31)	2553.58 (1015.5 to 4094.22)	0.19 (0.08 to 0.29)	3691.25 (1751.75 to 5484.77)	0.2 (0.1 to 0.3)	0.13 (−0.06 to 0.31)
Southeast Asia	76.91 (37.36 to 115.46)	0.02 (0.01 to 0.03)	292.49 (132.36 to 441.7)	0.04 (0.02 to 0.07)	2.57 (2.34 to 2.79)	563.72 (259.53 to 850.95)	0.12 (0.06 to 0.18)	2026.14 (909.33 to 3090.13)	0.3 (0.14 to 0.45)	2.44 (2.21 to 2.66)
Southern Latin America	94.69 (63.67 to 142.79)	0.2 (0.13 to 0.3)	416.36 (201.41 to 734.78)	0.54 (0.27 to 0.92)	3.54 (3.26 to 3.83)	664.4 (443.5 to 985.66)	1.36 (0.9 to 2.01)	2797.31 (1374.67 to 4853.66)	3.67 (1.86 to 6.14)	3.5 (3.23 to 3.78)
Southern Sub-Saharan Africa	17.71 (10.56 to 25.54)	0.03 (0.02 to 0.05)	54.66 (25.66 to 80.9)	0.07 (0.03 to 0.11)	2.95 (2.72 to 3.17)	131.5 (76.89 to 190.84)	0.23 (0.13 to 0.32)	395.25 (185.57 to 586.08)	0.5 (0.23 to 0.74)	2.96 (2.71 to 3.2)
Tropical Latin America	140.49 (101.61 to 203.96)	0.1 (0.07 to 0.15)	582.58 (263.54 to 949.61)	0.24 (0.11 to 0.39)	3.05 (2.69 to 3.42)	1023.4 (732.4 to 1491.83)	0.7 (0.49 to 1.03)	4024.86 (1856.01 to 6502.09)	1.7 (0.79 to 2.69)	3.02 (2.65 to 3.4)
Western Europe	958.69 (680.85 to 1465.58)	0.21 (0.15 to 0.31)	4504.64 (1296.68 to 11343.78)	0.62 (0.19 to 1.43)	3.72 (3.1 to 4.35)	6215.13 (4372.59 to 9533.74)	1.38 (0.99 to 2.13)	27907.46 (8288.93 to 68732.48)	4.11 (1.31 to 9.26)	3.69 (3.06 to 4.32)
Western Sub-Saharan Africa	736.01 (340.33 to 1056.6)	0.28 (0.13 to 0.41)	1620.09 (903.23 to 2214.9)	0.27 (0.14 to 0.39)	0.02 (−0.05 to 0.1)	5576.77 (2609.07 to 8032.41)	2.05 (0.96 to 3.02)	12254.27 (6755.1 to 16775.34)	1.98 (1.06 to 2.72)	−0.01 (−0.09 to 0.06)

UI uncertainty interval, *CI* confidence interval, *SDI* socio-demographic index, *ASR* age-standardized rate, *EAPC* estimated annual percentage change.

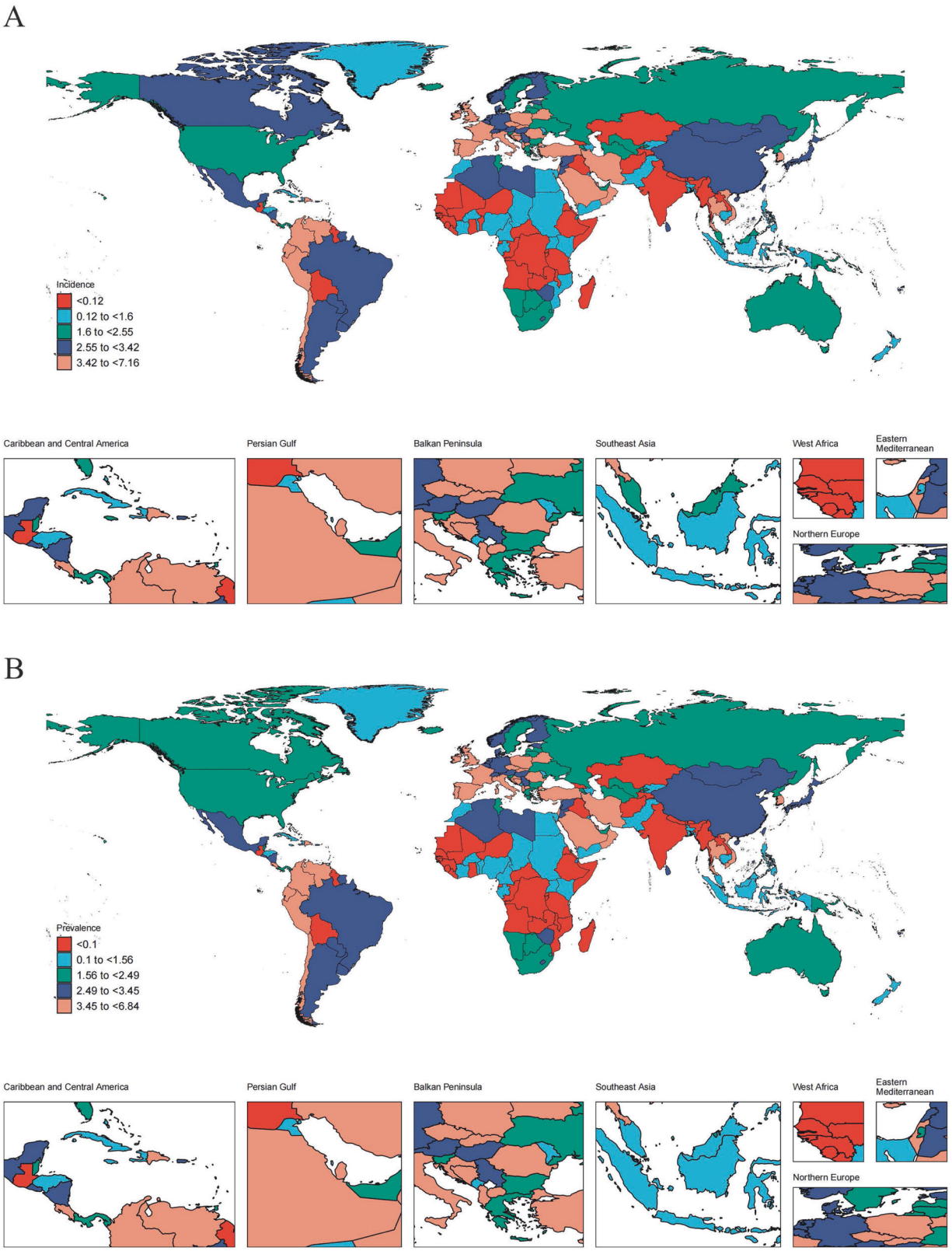

Fig. 1 The global disease burden of Burkitt lymphoma (BL) in countries and territories in 2021. A The age-standardized incidence rate of BL; (**B**) The age-standardized prevalence rate of BL.

2021 showed positive correlations with both SDI and HDI (Supplementary Fig. 9).

Globally, the incidence and prevalence of BL were primarily attributed to epidemiological changes, accounting for 52.38% and 53.90%, respectively (Supplementary Table 5, Supplementary Fig. 10). In contrast, mortality rates and DALYs were predominantly influenced by population growth. Among the 21 GBD regions, the contribution of aging was highest in the

DALYs of South Asia, particularly among females, while epidemiological changes contribute most significantly to DALYs in males of this region. Population growth has the most substantial impact on mortality rates in East Asia. The BAPC model projected that by 2030, the ASIR, ASPR, ASMR, and ASDR for BL will decline in both genders (Supplementary Fig. 11 and Supplementary Table 6).

We found that in 1990, the ASIR and ASPR were highest in Eastern Sub-Saharan Africa. However, by 2021, while some African countries continued to report high incidence rates, the highest ASIR for BL had shifted to High-income North America. This shift is likely attributable to advancements in medical technology and diagnostic capabilities. The reliability and effectiveness of diagnosis have been addressed in various editions of standardized recommendations for diagnosing BL [2]. In the 2008 revisions, significant diagnostic criteria were redefined in the 2008 revisions to include the introduction of the B-cell lymphoma unclassifiable category, which encompasses cases with features intermediate between BL and diffuse large B-cell lymphoma. This categorization was essential for accommodating cases that previously may have been misdiagnosed as Burkitt-like lymphoma. These improvements in diagnostic precision are likely contributors to the observed shift in BL incidence in regions with advanced medical technologies, such as North America. Additionally, in North America, the aging population structure may lead to increased incidence rates of certain cancers [10]. While BL predominantly affects younger individuals, rare cases in the elderly might become more apparent due to better survival rates.

Male BL patients are approximately twice as prevalent as female patients. This gender disparity may stem from genetic susceptibilities unique to males, particularly variants on the X or Y chromosomes. Somatic mutations in the genes *DDX3X* and *SOX11* on the X and Y chromosomes, respectively, corroborate these gender differences [11]. Additionally, mechanisms similar to the escape from X-inactivation tumor Suppressor syndrome may further explain the elevated incidence in males. We observed significant changes in the age distribution of BL. In 1990, BL predominantly affected children aged 5-9 years; by 2021, while this age group continued to exhibit a high incidence, there was a notable rise in incidence among individuals aged 65-79 years. This shift could be attributed to HIV infection, which compromises the immune system and potentially contributes to an increased incidence of BL in the elderly [12, 13]. The elevated incidence in children is likely linked to specific genetic mutations, such as *ARID1A*, whereas adult cases are often associated with different genetic alterations, including *TET2* [11, 14].

Globally, the incidence and prevalence of BL are primarily influenced by epidemiological changes. These changes may include variations in pathogen exposure, such as the strong association between EBV and BL [15], advancements in diagnostic techniques, and shifts in public health strategies. Concurrently, the growth in mortality and DALYs is mainly driven by population growth, indicating that an increase in population could lead to more individuals being at risk for BL, especially in densely populated areas. We predict that by 2030, the global incidence, prevalence, mortality rates, and DALYs of BL will demonstrate a declining trend. Advancements in treatment methods, particularly through developing new therapeutic strategies and medications, have improved the survival quality of patients with BL. Furthermore, advances in imaging and molecular diagnostic technologies have enabled the early diagnosis of BL, permitting treatments to commence at an earlier disease stage. In summary, we utilized the GBD database to provide a comprehensive overview of the epidemiological shifts and disease burden of BL from 1990 to 2021 and projected the disease burden into 2030.

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DATA AVAILABILITY

Data were obtained from the Global Health Data Exchange (GHDx) query tool (http://ghdx.healthdata.org/gbd-results-tool).

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ZT and WS revised the manuscript; YW wrote the first version of the manuscript; ZS, CH, and XX performed data analysis.

COMPETING INTERESTS
The authors declare no competing financial interests.

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