Estimates of the global burden of non-Hodgkin lymphoma attributable to HIV: a population attributable modeling study

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Summary

Background Human immunodeficiency virus (HIV) significantly increases the risk of non-Hodgkin lymphoma (NHL) development, yet the population-level impact on NHL burden is unquantified. We aim to quantify this association and estimate the global burden of HIV-associated NHL.

Methods In this meta-analysis, we searched five databases (PubMed, EMBASE, Cochrane Library, Web of Science, Scopus) from database inception up to September 13, 2023, identifying cohort, case–control, or cross-sectional studies with an effective control group to assess NHL risk among individuals with HIV infection, with two authors extracting summary data from reports. Global and regional HIV-associated population attributable fraction (PAF) and NHL disease burden were calculated based on the pooled risk ratio (RR). HIV prevalence and NHL incidence were obtained from the Joint United Nations Programme on HIV/AIDS (UNAIDS) and Global Burden of Diseases, Injuries, and Risk Factors Study 2019. Trends in NHL incidence due to HIV were assessed using age-standardised incidence rate (ASIR) and estimated annual percentage change (EAPC). This study was registered with PROSPERO (CRD42023404150).

Findings Out of 14,929 literature sources, 39 articles met our inclusion criteria. The risk of NHL was significantly increased in the population living with HIV (pooled RR 23.51, 95% CI 17.62–31.37; I^2 = 100%, p < 0.0001), without publication bias. Globally, 6.92% (95% CI 2.18%–11.57%) of NHL new cases in 2019 were attributable to HIV infection (30,503, 95% CI 9585–52,209), which marked a more than three-fold increase from 1990 (8340, 95% CI 3346–13,799). The UNAIDS region of Eastern and Southern Africa was the highest affected region, with 44.46% (95% CI 19.62%–58.57%) of NHL new cases attributed to HIV infection. The Eastern Europe and Central Asia region experienced the highest increase in ASIR of NHL due to HIV in the past thirty years, wherein the EAPC was 8.74% (95% CI 7.66%–9.84%), from 2010 to 2019.

Interpretation People with HIV infection face a significantly increased risk of NHL. Targeted prevention and control policies are especially crucial for countries in Eastern and Southern Africa, Eastern Europe and Central Asia, to achieve the UNAIDS's '90-90-90' Fast-Track targets. Limited studies across diverse regions and heterogeneity between research have hindered precise estimations for specific periods and regions.

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Keywords: HIV; Non-Hodgkin lymphoma; Risk ratio; Population attributable fraction; Global burden

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Research in context

Evidence before this study

We performed a systematic search in five databases (PubMed, EMBASE, Cochrane Library, Web of Science, and Scopus) from database inception up to September 13, 2023. The primary key words included "non-Hodgkin lymphoma", "NHL", "HIV", various NHL subtypes, and their respective equivalents. Previous research has reported that people living with human immunodeficiency virus (HIV) have a higher risk of developing non-Hodgkin lymphoma (NHL) compared to the population without HIV infection. However, no meta-analysis has quantified the worldwide and regional pooled incidence risks of NHL among individuals with HIV. Additionally, no study has estimated the global and regional incidence of HIV-associated NHL based on the population attributable fraction (PAF) modelling.

Added value of this study

This paper presents the first comprehensive pooled estimate of NHL risk derived from 39 articles, including people living with HIV (PLWH) from five regions defined by the Joint United Nations Programme on HIV/AIDS (UNAIDS) (Asia and the Pacific, Eastern and southern Africa, Latin America, Western and central Africa, Western and central Europe and North America). This study also provides global and regional estimates of the PAF of NHL in PLWH, and the burden (number and age-standardised rate of incidence) of NHL attributable to HIV infection.

Implications of all the available evidence

PLWH face a 23-fold increased risk of NHL compared to people without HIV infection. Globally, approximately 7% of NHL new cases in 2019 were attributable to HIV infection, representing a more than three-fold increase from 1990. Meanwhile, the burden of HIV-associated NHL varies widely by region; for instance, nearly 44% of NHL new cases were attributed to HIV infection in Eastern and Southern Africa. Meanwhile, the Eastern Europe and Central Asia region experienced the highest increase in age-standardised incidence rates of NHL due to HIV. However, 55 countries (55/189, 29.1%) have chosen not to disclose their HIV prevalence data, which limits the analysis at the global national level. Moreover, we could not calculate PAF stratified by regions within the periods with insufficient studies on specific time intervals across different regions. More studies are required to further evaluate burden of HIV-associated NHL between regions more accurately.

Introduction

Non-Hodgkin lymphoma (NHL) constitutes the predominant form of lymphoma, encompassing approximately 90% of all cases.[1,2] According to the GLOBOCAN database from the International Agency for Research on Cancer of the World Health Organization, among 36 different cancers, global NHL statistics for 2020 indicated 544,352 new cases and 259,793 new fatalities; the incidence of NHL ranked 8th and 10th for males and females, respectively.[3] Despite considerable research into NHL's aetiology, its mechanisms remain partially obscured.[2,4] Nevertheless, several risk factors for NHL have been identified, including viral infections (e.g., human T-cell leukaemia/lymphoma virus type I (HTLV-I) and Epstein–Barr virus (EBV), occupational and environmental exposures, genetic predisposition, and advanced age.[5,6]

NHL is among the acquired immunodeficiency syndrome (AIDS)-defining diseases, with HIV infection elevating NHL incidence and contributing to diverse NHL subtypes.[1,7,8] Although HIV does not directly cause NHL, due to impaired immune function in individuals with HIV infection, they are more susceptible to co-infections with HTLV-I and EBV.[5,6] Furthermore, due to immunosuppression pathogens like HTLV-I and EBV can more easily proliferate and replicate within the body, thereby triggering NHL.[9,10] The Joint United Nations Programme on HIV/AIDS (UNAIDS) reported 37.5 million adults (age ≥15 years) globally living with HIV in 2022.[11,12] Significant geographic variations in HIV prevalence pose challenges to the accessibility, reach, and effectiveness of preventive measures. Current assessments and forecasts indicate that the world is not making expectant progress to attain the UNAIDS '90-90-90' objectives.[13–15] Globally, with 76% of individuals with HIV having access to highly active antiretroviral therapy (ART), ART also has demonstrated efficacy in reducing the incidence of certain cancers such as Kaposi sarcoma and NHL, even as the burden of these traditionally age-associated cancers has increased.[16,17]

Although the close association between HIV and NHL has been established, there are few published articles that systematically quantify the association and estimate global and reginal burden of HIV-associated NHL in NHL high-burden setting. Despite the introduction of ART, which has contributed to a notable reduction in NHL incidence, HIV-associated NHL remains a significant source of morbidity and mortality in the individuals with HIV compared to the general population, because of heavy HIV burden and prominent disparity in coverage of ART.[11,18] Given to current high HIV prevalence, geographic disparities and the substantial burden of NHL, an assessment for the precise extent of HIV contribution to the burden of NHL is imperative.

This study performed a meta-analysis to comprehensively quantify the association between HIV infection and NHL. In addition, we aimed to provide an assessment of the global NHL burden attributed to HIV infection in individuals aged ≥15 years, using a population attributable fraction (PAF) model.[19–21] This assessment includes trends and disparities across various regions and countries. Moreover, we also explore the potential relationship between the burden of HIV-associated NHL and sociodemographic factors.

Methods

Search strategy and selection criteria

We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 guidelines.[22] The study protocol was registered on the PROSPERO (https://www.crd.york.ac.uk/prospero/; CRD 42023404150).

A systematic search was conducted in PubMed, EMBASE, Cochrane Library, Web of Science and Scopus from database inception up to September 13, 2023, following the PICOS principle (Supplementary Appendix 1). Primary key words included NHL (defined by International Classification of Diseases version 10th), HIV, and their respective equivalents (detail information available at Supplementary Appendix 1). Studies meeting inclusion criteria and providing relevant risk measures risk ratio (RR), odds ratio (OR), standardised incidence rate (SIR) with corresponding 95% confidence interval (CI) were extracted.

Literature screening was conducted using Endnote software (version X9.2). Data extraction and quality assessment were independently conducted by YC and JHZ, with discrepancies resolved through consultation or arbitration by ZWW. Additional details are available in (Supplementary Table S1). An 11-item checklist recommended by the Agency for Healthcare Research and Quality (AHRQ) (https://www.wjx.cn/m/85284180.aspx) was used to categorise the included articles into high-, middle-, and low-risk levels corresponding to low-, middle-, and high-quality in sequence.

Data analysis

HIV prevalence data for adults aged ≥15 years from 1990 to 2019 were sourced from UNAIDS (https://aidsinfo.unaids.org/). UNAIDS categorised the 189 UN member states into eight regions and 55 of them did not disclose HIV prevalence data (Supplementary Tables S2 and S3). Incidence number, stratified by age (≥15 years) was obtained for 204 countries and territories through the Global Health Data Exchange query tool (https://vizhub.healthdata.org/gbd-results/). The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) database employed a five-tier socio-demographic index (SDI) to categorise the 204 locations into low, low-middle, middle, high-middle, and high regions (https://ghdx.healthdata.org/search/site/SDI) (Supplementary Table S4).

We calculated a pooled RR with a corresponding 95% CI to assess the association between HIV and NHL according a random-effects model. A chi-squared test on Cochrane's Q statistic was used to evaluate the heterogeneity, with a quantitative Higgins's I^2 value. We undertook subgroup analyses and meta-regression trying to find the source of heterogeneity, based on the characters of study region, study type, study setting, study period, NHL subtype, and sex. Hartung-Knapp-Sidik-Jonkman method was performed when the number of included studies is low (≤5) in the sub-group meta-analysis.[23,24] In the meta-analysis, we considered RR, OR, and SIR to be equivalent in our pooled estimates, since NHL can be considered a rare outcome.[25] We employed external estimates to account for potential confounding biases for studies did not report adjusted estimates.[26] Sensitivity analyses were performed by omitting study one-by-one, or those with high risk levels. Egger's linear regression and funnel plot were used to explore potential publication bias. The amendment of bias was achieved through the trim-and-fill method. Meta-analyses were performed using R software (version 4.2.2) through the package 'metafor'.

Using study period and UNAIDS region specific pooled RR values (Supplementary Table S5) and HIV prevalence data from UNAIDS, we calculated the PAF (%) through the Levin's Formula (1)[27,28]:

$$PAF = \frac{HIV\ prevalence * (RRa\text{-}1)}{1 + HIV\ prevalence * (RRa\text{-}1)} \quad (1)$$

where RRa represented the adjusted relative risk. Moreover, we compared the results of PAF calculated with Levin's and Miettenen's formulas, respectively, and performed a correlation analysis using a Spearman test. Considering the ideal world where it is not practically feasible to completely eliminate HIV exposure, we calculated generalized impact fractions (GIF) to assess the benefits of reducing the prevalence of HIV by 1%, 20%, 40%, 60%, 80%, and 100% in preventing NHL.[29,30]

When calculating the PAF/GIF, we propagated the pooled RR and HIV prevalence data to fit log-normal and beta distributions, respectively. To ascertain 95% CI, we conducted 10,000 calculations using R software (Supplementary Appendix 2). Age-standardised incidence rate (ASIR) per 100,000 population of incidence and the corresponding 95% CI were calculated from 1990 to 2019, based on the age-specific all-cause NHL incidence, and the world standard population, as reported in GBD 2019 (Supplementary Appendix 3).[31] The HIV-associated incidence numbers and ASIR were derived by multiplying the all-cause numbers and ASIR by the corresponding PAF. To illustrate the specific

calculation process, we provided an example using data from Zimbabwe (Supplementary Figs. S1 and S2).

We utilized an estimated annual percentage change (EAPC) with 95% CI to assess the trend in ASIR from 1990 to 2019 using a regression model fitted by logarithmic ASIR, as indicated below (y is the age-standardised incidence rate, x is the calendar year) (Supplementary Appendix 3)[32]:

$$ln(y) = \alpha + \beta x + \varepsilon \quad (2)$$

$$EAPC_{with\ 95\%\ CI} = 100 * \left[exp(\beta) - 1\right] \quad (3)$$

When the lower boundary of 95% CI for the corresponding EAPC is above 0, ASIRs are indicative of increasing trends; the upper boundary of 95% CI for the corresponding EAPC is below 0, the rates signify decreasing trends. Otherwise, ASIRs remain stable from 1990 to 2019. The association between SDI score and all-cause or HIV-associated ASIR and EAPC were estimated using a Spearman test based on R software (version 4.2.2).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. ZWW and JHZ have full access to all the data in the study and have final responsibility for the decision of submission to the journal for publication.

Results

Screening, characteristics, and quality assessment of included studies

Following a systematic search across five databases, 39 articles were finally deemed suitable for inclusion in the meta-analysis (Fig. 1). Characteristics of the 50 studies (deriving from 39 articles: 20 cohort studies, 5 case–control studies, and 14 registry linkage studies) were summarised in Table 1. More information is available at Supplementary Table S6. Ten articles just provided crude (unadjusted) values while 29 studies performed adjusted OR, RR, or SIR values (Supplementary Table S7). Participant numbers spanned from 89 to 448,258, with study periods ranging from 1970 to 2018 and publication years spanning from 1997 to 2022. A majority of (30, 76.9%) studies constituted multi-centre designed, with 23 (59.0%) studies conducted in Western and central Europe and North America. Based on the recommended 11-item checklist from AHRQ, the 39 articles were categorised into 1 high-risk, 32 middle-risk, and 6 low-risk studies (Supplementary Table S8).

Risk of NHL in people living with HIV

50 estimates were extracted from the 39 articles to perform the meta-analysis. Results indicated that the population with HIV had a significantly increased relative risk of NHL (pooled RR 23.51, 95% CI 17.62–31.37) compared to those uninfected, with notable heterogeneity (I^2 = 100%, p < 0.0001) under a random-effects model (Fig. 2). Significant subgroup difference of study region, study type, risk level, and study period were found by subgroup analysis. In detail, Eastern and southern African studies were reported a significantly lower risk of NHL (RR 4.86, 95% CI 3.21–6.50), as well as Western and central Africa (RR 3.78, 95% CI 2.15–5.41, Supplementary Table S9). In the remaining three UNAIDS regions, corresponding risk levels ranged from 13.72 to 30.31, with overlapping 95% CIs. RR value from case–control studies (3.72, 95% CI 2.62–4.81) were also significantly lower than those from cohort studies (27.85, 95% CI 19.83–39.11) and linkage studies (28.89, 95% CI 18.54–45.00, Supplementary Table S9). In addition, we found a decrease trend of study period form 1980–1989 (65.68, 95% CI 46.88–92.02) to 2010–2019 (13.16, 95% CI 4.87–21.45). Meta-regression analysis reveals these characteristics could each explain 21%–30% sources of heterogeneity (Supplementary Table S10). We still estimated the pooled RR values from 12 unadjusted studies (RR 23.42, 95% CI 12.69–43.22), with no significant difference to the 38 adjusted studies (RR 21.63, 95% CI 15.60–30.00), even the external adjusted RR value (RR 30.76, 95% CI 16.72–56.62) (Supplementary Table S11). In addition, NHL risk in males (RR 29.98, 95% CI 16.82–53.44) was slightly higher than it in females (RR 21.62, 95% CI 11.59–40.34), although no significant difference found (Supplementary Table S9). And more information of studies for male and female is available at Supplementary Table S12. Similar results were found in Burkitt NHL group (RR 82.14, 95% CI 35.97–128.32), which is non-significantly higher than other types (Supplemantary Tables S9 and S13).

Sensitivity analysis involving the systematic omission of one study at a time, including a high-risk level study demonstrated no significant change in the pooled RR value (Supplementary Fig. S3). Similar results were observed in middle-risk and low-risk studies with overlapping CIs (Supplementary Table S14). Additionally, assessment for publication bias using a symmetric funnel plot (Supplementary Fig. S4) and Egger's test (t = –0.50; p = 0.62) yielded no evidence thereof.

Global burden of HIV-associated NHL

From 1990 to 2019, the global PAF raised from 4.72% (95% CI 1.89%–7.71%) in 1990 to 6.92% (95% CI 2.18%–11.57%) in 2019 among individuals aged ≥15 years (Table 2). Specific PAFs calculated by study periods and sex were shown in Supplemantary Tables S15 and S16. The rise of PAF correlated with over a three-fold increase in HIV-associated NHL new cases, ascending from 8340 (95% CI 3346–13,799) to 30,503 (95% CI 9585–52,209) (Table 2, Supplementary

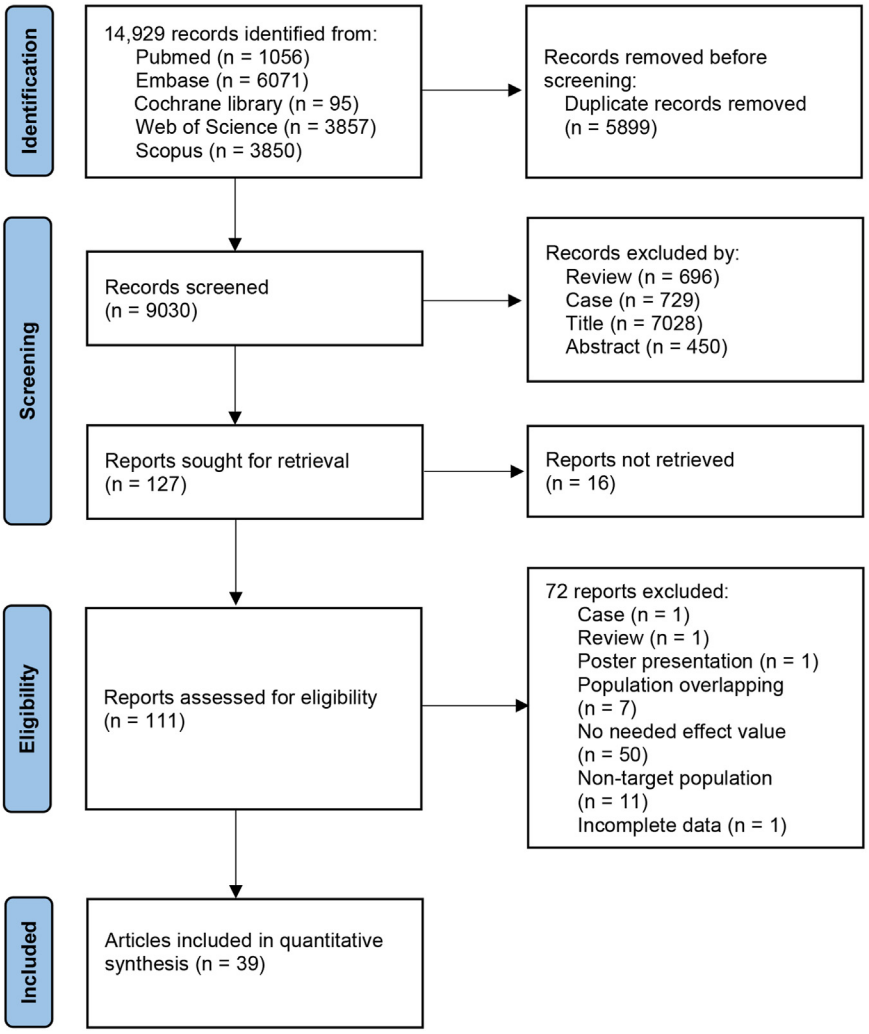

***Fig. 1:* PRISMA flow chart for study selection**. PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses.

Table S17). In addition, the global HIV-associated ASIR (per 100k population) increased from 2010 to 2019 (Fig. 3C), demonstrating an EAPC of 1.19% (95% CI 1.09%–1.29%) (Fig. 4). Meanwhile, stable trend at the global level was observed for all-cause ASIR in the period (Supplemantary Fig. S5), with a EAPC of 0.19% (95% CI 0.11%–0.27%) (Fig. 4). EAPCs of 1990–1999 and 2000–2009 were available at Supplementary Fig. S6. Based on correlation analysis, there was no significant difference in PAF calculated by Levin's and Miettenen's formulas (Supplementary Table S18 and Supplementary Fig. S7). The GIF by assumed realistic interventions of 1%, 20%, 40%, 60%, 80%, and 100% reduction of HIV prevalence were calculated (Supplementary Table S19 and Supplementary Fig. S8).

HIV-associated NHL burden exhibited regional disparities across eight UNAIDS regions, with Eastern and southern Africa experienced the highest PAF (44.46%, 95% CI 19.62%–58.57%), with 3104 new cases (95% CI 1282–5011) in 2019 (Fig. 5A and Supplementary Table S17). Correspondingly, this region also had the highest HIV-associated ASIR (1.78, 95% CI 0.78–2.34) (Fig. 5B). Meanwhile, Western and central Europe and North America had the highest HIV-associated number (53.29, 16.42–97.20) (Fig. 5C). From 2010 to 2019, increased HIV-associated ASIR was observed in eight UNAIDS regions, except for Western and central Africa (Figs. 3 and 4). Specially, the Eastern Europe and central Asia region was noted the most significant increase trend (EAPC 8.74%, 95% CI 7.66%–9.84%), as well as period 1990–1999, and 2000–2009 (Figs. 3 and 4, Supplementary Fig. S6). Additionally, all-cause ASIR for NHL remained stable or slightly changed across regions (Fig. 4, Supplementary Figs. S5 and S6). Specific PAFs calculated by specific RRs for five included UNAIDS-defined regions were shown in Supplementary Table S20.

Author and year[a]	Country	Study type	Number of participants	Number of NHL cases	Study period	Risk level	Effect value type
Sitas et al., 1997	South Africa	CCS	1238	40	1992–1995	Middle risk	OR
Serraino et al., 1997	Italy	Cohort study	1255	15	1980–1995	Middle risk	SIR
Franceschil et al., 1998	Italy	Registry linkage study	6067	111	1976–1994	Middle risk	SIR
Cooksley et al., 1999	America	Cohort study	2289	394	1985–1994	Low risk	SIR
Petruckevitch et al., 1999	UK	Registry linkage study	992	3	1982–1995	Middle risk	SIR
Grulich et al., 1999	Australia	Cohort study	3616	205	1980–1993	Middle risk	SIR
Sitas et al., 2000	South Africa	CCS	5727	105	1995–1999	Middle risk	OR
Gallagher et al., 2001	America	Registry linkage study	10,083	2434	1981–1994	Middle risk	SIR
Gallagher et al., 2001	America	Registry linkage study	1288	342	1981–1994	Middle risk	SIR
Frisch et al., 2001	America	Registry linkage study	302,834	3344	1978–1996	Low risk	SIR
Wilde et al., 2002	UK	Cohort study	89	67	1978–1999	High risk	SIR
Frisch et al., 2003	Denmark	Cohort study	5005	32	1989–1997	Middle risk	SIR
Hessol et al., 2004	America	Cohort study	1950	12	1994–2001	Middle risk	SIR
Newnham et al., 2005	UK	Registry linkage study	33,190	86	1985–2001	Middle risk	SIR
Busnach et al., 2006	France/Italy	Cohort study	8074	201	1970–2005	Middle risk	SIR
Mbulaiteye et al., 2006	Uganda	Registry linkage study	12,607	5	1988–2002	Middle risk	SIR
Engels et al., 2006	America	Registry linkage study	107,417	560	1996–2002	Middle risk	SIR
Galceran et al., 2007	Spain	Registry linkage study	1304	52	1981–1999	Middle risk	SIR
Srisawat et al., 2008	Thailand	Cohort study	863	1	1997–2007	Middle risk	SIR
Dhir et al., 2008	India	Cohort study	166	63	2001–2005	Middle risk	SIR
Dhir et al., 2008	India	Cohort study	85	14	2001–2005	Middle risk	SIR
van Leeuwen et al., 2009	Australia	Cohort study	20,232	370	1982–1995	Low risk	SIR
van Leeuwen et al., 2009	Australia	Cohort study	20,232	170	1996–1999	Low risk	SIR
van Leeuwen et al., 2009	Australia	Cohort study	20,232	121	2000–2004	Low risk	SIR
Silverberg et al., 2009	America	Cohort study	222,590	422	1996–2007	Middle risk	RR
Dal Maso et al., 2009	Italy	Registry linkage study	21,951	352	1997–2004	Low risk	SIR
Seaberg et al., 2010	America	Cohort study	6949	194	1984–2007	Low risk	SIR
Vajdic et al., 2010	Australia	Cohort study	17,175	661	1982–2004	Middle risk	SIR
Lanoy et al., 2010	America	CCS	149,630	1836	1987–2002	Middle risk	OR
Franceschi et al., 2010	Swiss	Registry linkage study	9429	191	1985–1996	Middle risk	SIR
Franceschi et al., 2010	Swiss	Registry linkage study	9429	52	1997–2001	Middle risk	SIR
Franceschi et al., 2010	Swiss	Registry linkage study	9429	32	2002–2006	Middle risk	SIR
Zhang et al., 2011	China	Cohort study	3554	18	2004–2008	Middle risk	SIR
Tanon et al., 2012	Côte d'Ivoire/Benin	CCS	1459	119	2009–2011	Middle risk	OR
Hleyhel et al., 2013	France	Cohort study	99,309	1078	1992–1996	Middle risk	SIR
Hleyhel et al., 2013	France	Cohort study	99,309	511	1997–2000	Middle risk	SIR
Hleyhel et al., 2013	France	Cohort study	99,309	368	2001–2004	Middle risk	SIR
Hleyhel et al., 2013	France	Cohort study	99,309	387	2005–2009	Middle risk	SIR
Chen et al., 2014	China	Cohort study	15,269	214	1998–2009	Low risk	SIR
Jaquet et al., 2015	Côte d'Ivoire/Benin/ Nigeria/Togo	CCS	2436	133	2009–2012	Middle risk	OR
Salters et al., 2016	Canada	Cohort study	2211	19	1994–2008	Middle risk	SIR
Godbole et al., 2016	India	Registry linkage study	613	15	1996–2008	Middle risk	SIR
Lee et al., 2016	America	Cohort study	63,221	182	2006–2012	Middle risk	SIR
Hernández-Ramírez et al., 2017	America	Registry linkage study	448,258	3687	1996–2012	Middle risk	SIR
Tanaka et al., 2017	Brazil	Registry linkage study	1461	304	1997–2012	Middle risk	SIR
Tanaka et al., 2017	Brazil	Registry linkage study	539	96	1997–2012	Middle risk	SIR
Hessol et al., 2018	America	Registry linkage study	22,623	848	1985–2013	Middle risk	SIR
Park et al., 2022	South Korea	Cohort study	10,444	67	2006–2018	Middle risk	SIR
Park et al., 2022	South Korea	Cohort study	1108	6	2006–2018	Middle risk	SIR
Lee et al., 2022	South Korea	Cohort study	11,737	98	2004–2017	Middle risk	SIR

[a]50 estimates from the 39 included articles that provided for estimating pooled RR value of NHL in patients with HIV compared with population without HIV infection. Abbreviations: HIV, human immunodeficiency virus; NHL, non-Hodgkin lymphoma; CCS, case–control study; RR, risk ratio; OR, odds ratio; SIR, standardised incidence rate.

Table 1: **Characteristics of 50 studies deriving from 39 eligible articles.**

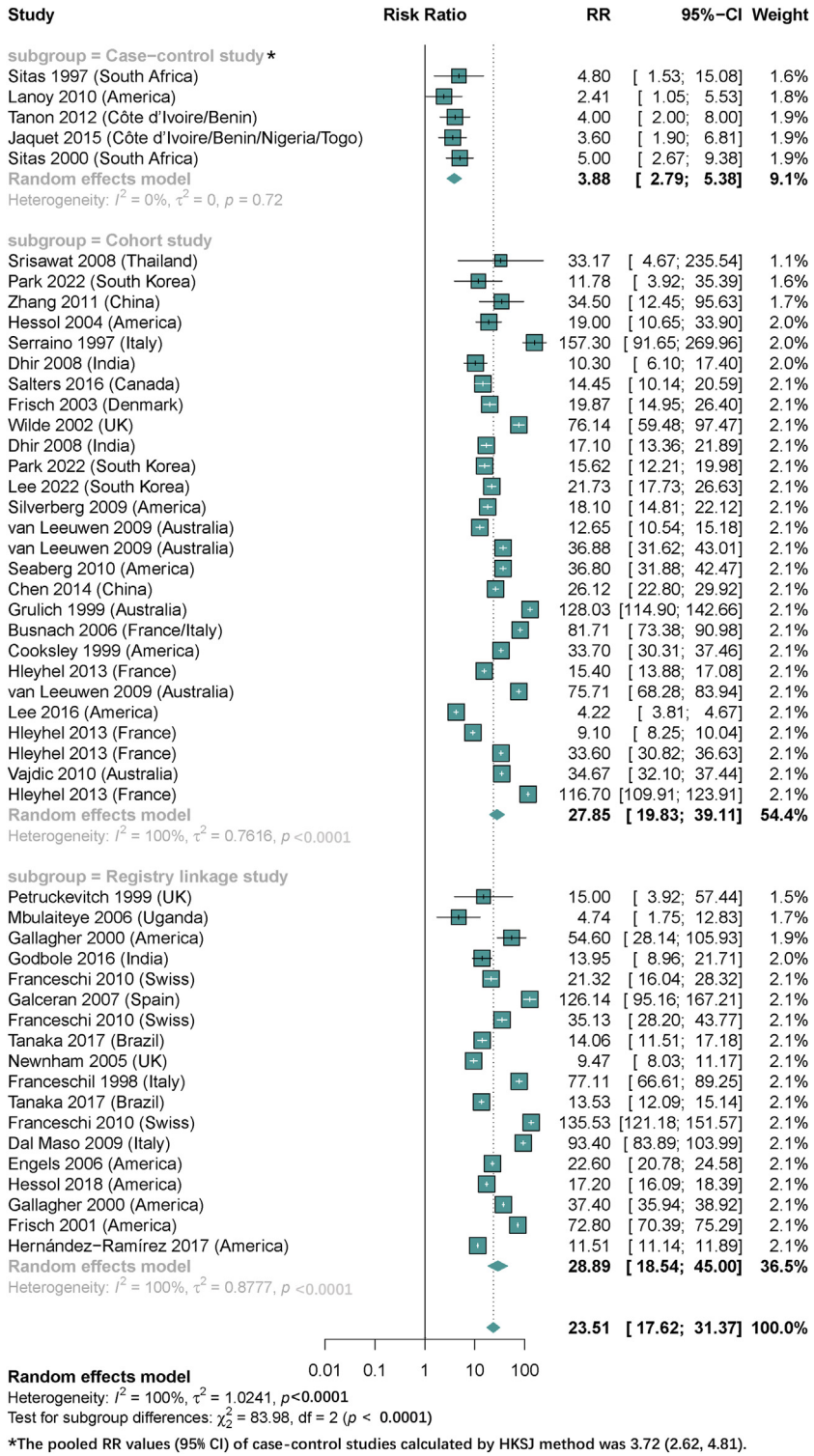

Fig. 2: **Forest plot showing the pooled risk ratio of NHL in population with HIV infection compared to people without HIV**. NHL, non-Hodgkin lymphoma; HIV, human immunodeficiency virus; RR, risk ratio; HKSJ, Hartung-Knapp-Sidik-Jonkman.

UNAIDS region	HIV prevalence (%)		PAF (%)		All-cause ASIR (per 100k)		HIV-associated ASIR (per 100k)	
	1990	2019	1990	2019	1990	2019	1990	2019
Global	0.21 (0.17, 0.25)	0.62 (0.50, 0.75)	4.72 (1.89, 7.71)	6.92 (2.18, 11.57)	6.19 (6.16, 6.22)	7.72 (7.70, 7.74)	0.29 (0.12, 0.48)	0.53 (0.17, 0.89)
Asia and the Pacific	0.04 (0.03, 0.05)	0.17 (0.13, 0.21)	0.99 (0.38, 1.68)	1.97 (0.61, 3.47)	3.47 (3.44, 3.50)	6.15 (6.13, 6.18)	0.03 (0.01, 0.06)	0.12 (0.04, 0.21)
Caribbean	0.58 (0.50, 0.69)	1.04 (0.89, 1.22)	12.29 (5.13, 18.85)	11.24 (3.77, 18.05)	6.47 (6.09, 6.90)	6.81 (6.52, 7.11)	0.79 (0.33, 1.22)	0.76 (0.25, 1.23)
Eastern and southern Africa	3.12 (2.53, 3.71)	6.72 (5.46, 8.00)	42.35 (21.92, 55.51)	44.46 (19.62, 58.57)	3.40 (3.26, 3.55)	4.00 (3.90, 4.11)	1.44 (0.75, 1.90)	1.78 (0.78, 2.34)
Eastern Europe and central Asia	0.00 (0.00, 0.00)	0.63 (0.57, 0.71)	0.03 (0.01, 0.06)	7.15 (2.32, 11.64)	3.24 (3.17, 3.32)	5.27 (5.19, 5.36)	0.00 (0.00, 0.00)	0.38 (0.12, 0.61)
Latin America	0.13 (0.09, 0.17)	0.45 (0.30, 0.58)	2.83 (1.09, 5.04)	4.84 (1.49, 8.77)	4.26 (4.17, 4.36)	6.13 (6.06, 6.21)	0.12 (0.05, 0.21)	0.30 (0.09, 0.54)
Middle East and North Africa	0.01 (0.00, 0.01)	0.07 (0.06, 0.09)	0.15 (0.06, 0.26)	0.86 (0.26, 1.54)	3.49 (3.37, 3.62)	5.37 (5.28, 5.47)	0.01 (0.00, 0.01)	0.05 (0.01, 0.08)
Western and central Africa	1.02 (0.84, 1.25)	1.32 (1.09, 1.62)	19.67 (8.63, 29.31)	13.84 (4.61, 22.05)	2.51 (2.40, 2.63)	2.87 (2.79, 2.95)	0.49 (0.22, 0.74)	0.40 (0.13, 0.63)
Western and central Europe and North America	0.14 (0.12, 0.16)	0.27 (0.23, 0.31)	4.16 (1.27, 7.15)	3.08 (0.96, 5.28)	12.83 (12.75, 12.92)	13.57 (13.51, 13.64)	0.53 (0.16, 0.92)	0.42 (0.13, 0.72)

Abbreviations: HIV, human immunodeficiency virus; NHL, non-Hodgkin lymphoma; PAF, population attributable fraction; UNAIDS, Joint United Nations Programme on HIV/AIDS; ASIR, age-standardised incidence rate.

Table 2: **Population attributable fraction using prevalence data of HIV for the group of age ≥15 years and age-standardised NHL incidence rates with HIV-associated ones by regions.**

Based on HIV prevalence data from UNAIDS encompassing 134 countries, Swaziland displayed the highest PAF (76.95%, 95% CI 51.84%–85.07%) in 2019 in the ≥15 years population group, followed by Lesotho (73.42%), Botswana (72.68%), South Africa (66.46%), and Namibia (61.07%) (Supplementary Table S21). Notably, from 2010 to 2019, the top ten countries with the highest PAF were all situated in Eastern and southern Africa, except for the tenth Equatorial Guinea was in Western and central Africa (Supplementary Table S21). Among the 134 countries, 91 (67.91%) countries exhibited an increasing trend in ASIR due to HIV from 2010 to 2019, with most countries with the highest increases located in Eastern Europe and Central Asia (Georgia, Tajikistan, Albania, Kyrgyzstan), and Middle East and North Africa (Egypt, United Arab Emirates, Algeria, and Saudi Arabia) (Supplementary Table S22).

We further estimated the association between SDI and burden of HIV-associated NHL at the national level. A significant positive correlation emerged between SDI score and all-cause ASIRs in 2019 (Fig. 6A, r = 0.66, 95% CI 0.56–0.75, p < 0.0001) but no significant association was observed with HIV-associated ASIRs (Fig. 6B, r = –0.061, 95% CI –0.23 to 0.11, p = 0.49). Meanwhile, no significant association was presented between SDI score and EAPCs (from 2010 to 2019) of all-cause ASIRs (Fig. 6C, r = –0.074, 95% CI –0.24 to 0.10, p = 0.41), but a positive correlation was observed with EAPCs (from 2010 to 2019) of HIV-associated ASIRs (Fig. 6D, r = 0.47, 95% CI 0.27–0.64, p < 0.0001).

Discussion

Our study represents a comprehensive assessment of the association between HIV infection and NHL risk, providing the first-ever evaluation of the global burden of HIV-related NHL. The key findings are as follows: first, people living with HIV (PLWH) faced a 23-fold higher risk of developing NHL compared to those without HIV. Second, a significant more than three-fold increase of HIV-associated NHL new cases from 1990 to 2019, underscored an escalating global trend in the burden of HIV-associated NHL. Third, the burden of HIV-associated NHL exhibited substantial regional variation, with the highest observed within Eastern and Southern Africa. Fourth, middle- and high-middle SDI countries, especially those in Eastern Europe and Central Asia, experienced the highest increase in the incidence of NHL due to HIV.

Our meta-analysis demonstrated a significant higher risk in PLWH compared to those without HIV infection. Studies have reported NHL is one of the main types of lymphoma developed in the population with HIV.[33] Several studies have reported that HIV infection plays a significant role in NHL pathogenesis, including

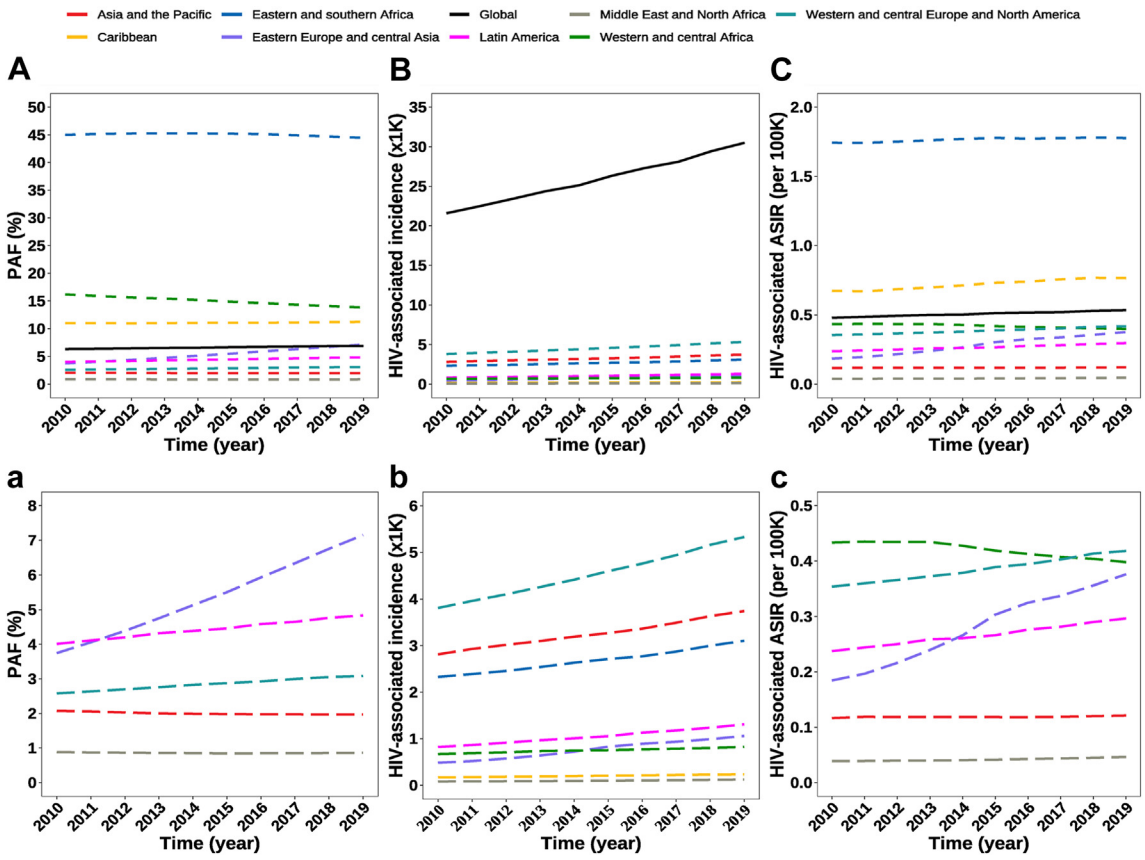

Fig. 3: **The trend of PAF, HIV-associated incidence, and HIV-associated ASIR for the global and eight UNAIDS-defined regions from 2010 to 2019**. A, population attributable fraction (PAF, %); B, incidence number due to HIV (×1000); C, HIV-associated age-standardised incidence rate (ASIR) per 100,000 population. a, b, and c showing changing trends more clearly corresponding A, B, and C, respectively. HIV, human immunodeficiency virus; UNAIDS, Joint United Nations Programme on HIV/AIDS.

impaired immune system, genetic alterations, chronic B cell activation, and viral infection.[34–36] Firstly, the gradual depletion of early, naive, and memory $CD4^+$ T-lymphocyte populations by HIV compromises both innate and adaptive immunity.[37–39] Consequently, $CD4^+$ T cell depletion leads to impaired immunological function, reducing neoplasm immunologic monitoring and immune clearance, thereby creating a favourable environment for NHL development. Additionally, HIV may also directly or indirectly promote genetic mutations and lymphoma cell proliferation, leading to NHL.[40–43] Moreover, chronic B-cell activation facilitated by HIV-mediated immunological failure, which is responsible for hypergammaglobulinemia, impaired humoral immunity, and florid germinal centre hyperplasia, has been linked to lymphoma formation.[44] Furthermore, patients with HIV are more susceptible to virus co-infections such as EBV, which has been recognised a risk factor for NHL, by directly down-regulate the transcription of cellular NHL tumour suppressor genes, such as BLIMP1.[6,7,45]

Sub-group analysis found a decrease trend of RR values according to the study period from 1980 to 2019, although overlap confidence interval exited between majority groups. Such results are likely primarily attributable to the widespread adoption of ART therapy, which has lowered the risk of NHL occurrence.[46] In addition, EBV has been reported a higher prevalence (more than 60%) in Burkitt NHL and coinfected with HIV by difference countries,[47,48] which could indirectly interpret our result that the RR value is higher in Burkitt NHL. Moreover, significant lower RR values were observed in Eastern and southern Africa, and Western and central Africa, compared with the other three UNAIDS regions (Asia and the Pacific, Latin America, Western and central Europe and North America). The regional disparities can be explained by the following factors: first, there was no eligible study coming from three of the eight UNAIDS regions (Eastern Europe and central Asia, Middle East and North Africa, and Caribbean) and insufficient studies included in another three regions (Eastern and southern Africa, Western and

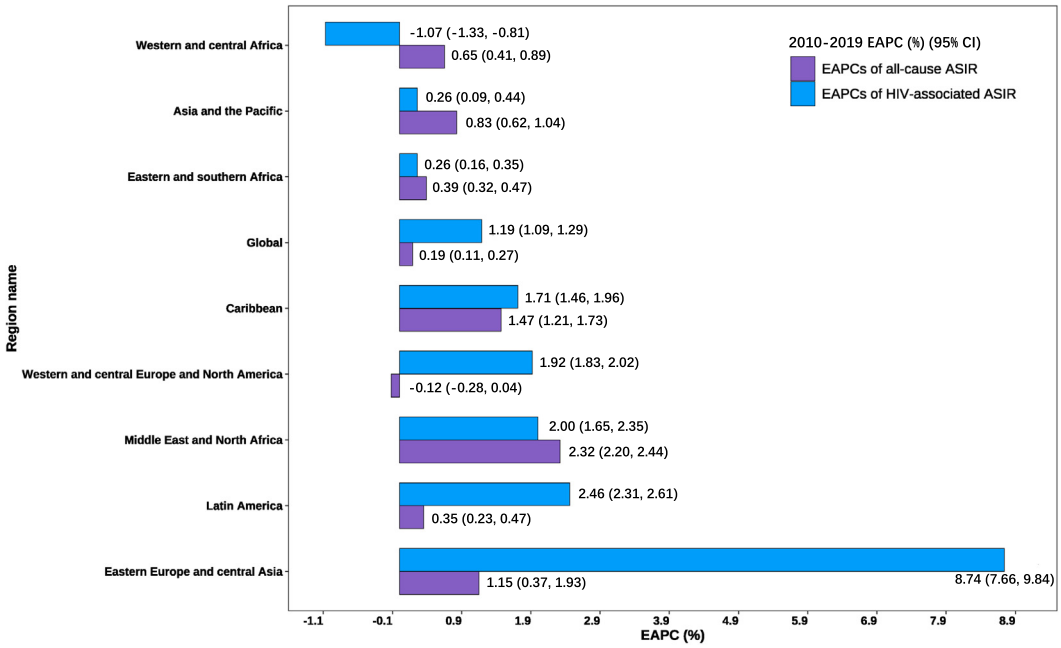

Fig. 4: **The EAPC of all-cause and HIV-associated ASIR for the global and eight UNAIDS-defined regions from 2010 to 2019**. EAPC, estimated annual percentage change; HIV, human immunodeficiency virus; ASIR, age-standardised incidence rate; UNAIDS, Joint United Nations Programme on HIV/AIDS.

central Africa, and Latin America), which may lead to inaccurate estimates. Second, discrepancy of HIV testing method, NHL diagnosis period, and combination ART coverage between countries may derive the heterogeneity of the regional RR values.[49–51] Third, the absence of screening in included participants for certain infectious agents that are likely to promote the development of NHL (such as EBV and hepatitis C virus (HCV)), could impact the regional estimation of pooled RR. For example, EBV has been reported as an established cause of Burkitt lymphoma (BL), with 95% of cases with EBV distribution in the equatorial belt of Africa.[52,53] Meanwhile, evidences have reveal a causative relationship between HCV and NHL,[54] with Sub-Saharan Africa exhibiting high burden of HCV and a national prevalence of 5.3%.[55,56]

Our findings revealed that HIV-associated NHL accounted for approximately 7% of the global NHL cases, with the Eastern and Southern Africa bearing the highest burden attributable to HIV-infection. Although, significant progress has been made towards achieving the '90-90-90' UNAIDS Fast-Track targets in Eastern and Southern Africa, the persistently high burden of HIV highlights the need for continued efforts. While some countries, such as Eswatini, Namibia, and Zambia, have made strides in meeting the targets, others, like Mauritius and South Sudan, face more limited advancements, resulting in varied percentages (ranging from 15% to 98%) of people being aware of their HIV status.[57] A study by Borges in 2017 demonstrated that the early initiation of ART can reduce the risk of NHL.[50] Nevertheless, the rates of ART reception vary significantly (from 37% to 98%) between countries,[57] underscoring profound health service disparities within and across nations. Nevertheless, we observed a stable burden of HIV-related NHL in Eastern and Southern Africa over the last 20 years, following a significant increase in the preceding decade. This suggests that directing global medical resources towards achieving the UNADIS Fast-Track targets could effectively alleviate both HIV and HIV-related NHL burdens in this region. Furthermore, considering that EBV infection increases the risk of BL especially for population with HIV, the development of an EBV virus vaccine is expected to be helpful for HIV-associated NHL disease burden. According to research, the EBV gp350-Ferritin nanoparticle vaccine (under trials) is expected to reduce the burden of HIV-associated NHL in the future.[58,59]

Significantly, the burden of HIV-associated NHL demonstrated the fastest increase in the Eastern Europe and central Asia in the past thirty years, wherein the EAPC of HIV-associated NHL ASIR reached approximately 9% from 2010 to 2019. On the contrary, its all-cause burden remained stable. These results suggest that HIV may have become a primary contributing factor to the burden of NHL in the Eastern Europe and central Asia. UNAIDS has also reported that the region

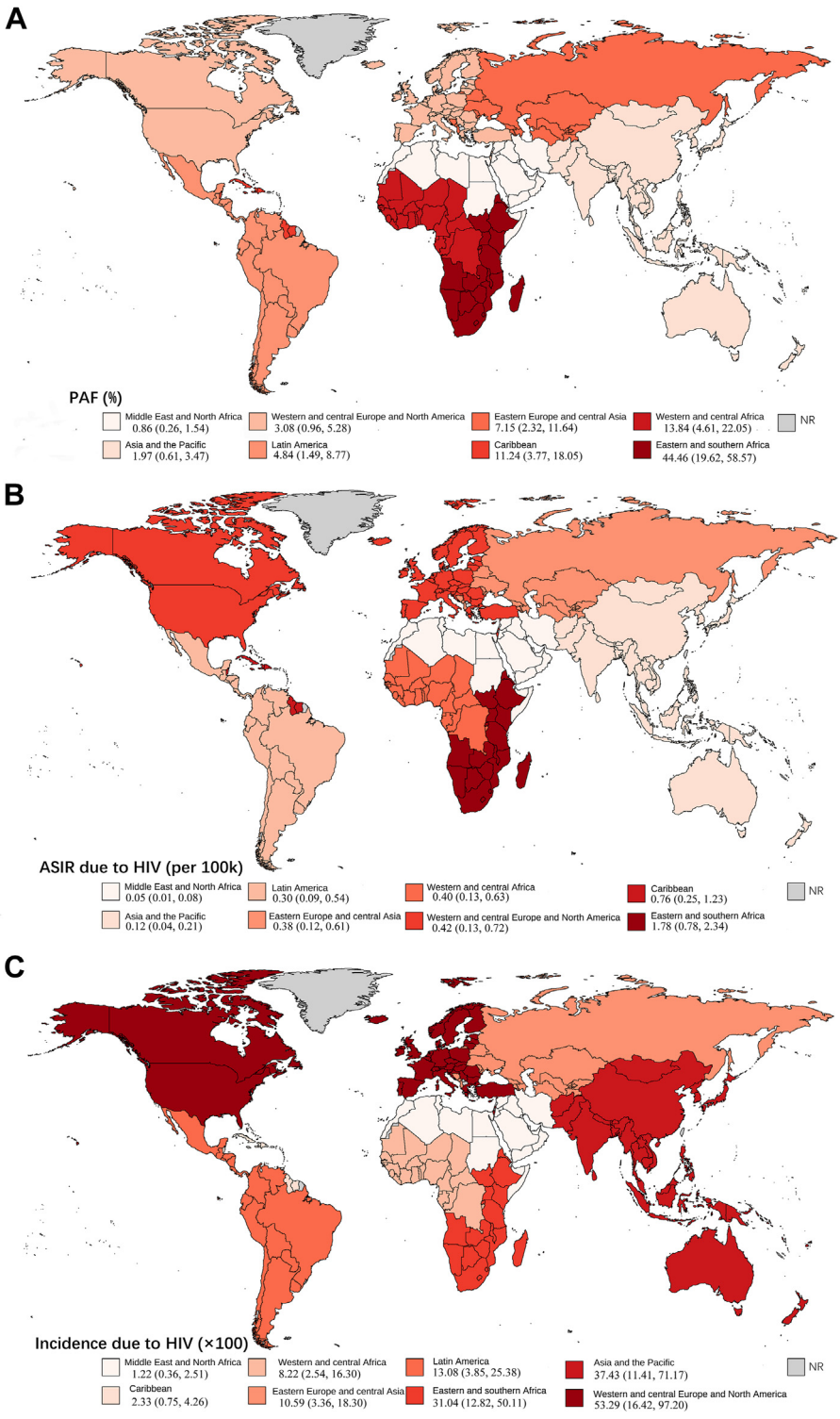

Fig. 5: **Map of PAF, HIV-associated ASIR, and incidence number due to HIV for the eight UNAIDS-defined regions in 2019**. A, population attributable fraction (PAF, %); B, HIV-associated age-standardised incidence rate (ASIR) per 100,000 population; C, incidence number due to HIV (×100). The darker colour lump represents heavier NHL burden in the map and the grey lump represents that data of the region was not reported. HIV, human immunodeficiency virus; UNAIDS, Joint United Nations Programme on HIV/AIDS; NR, not reported.

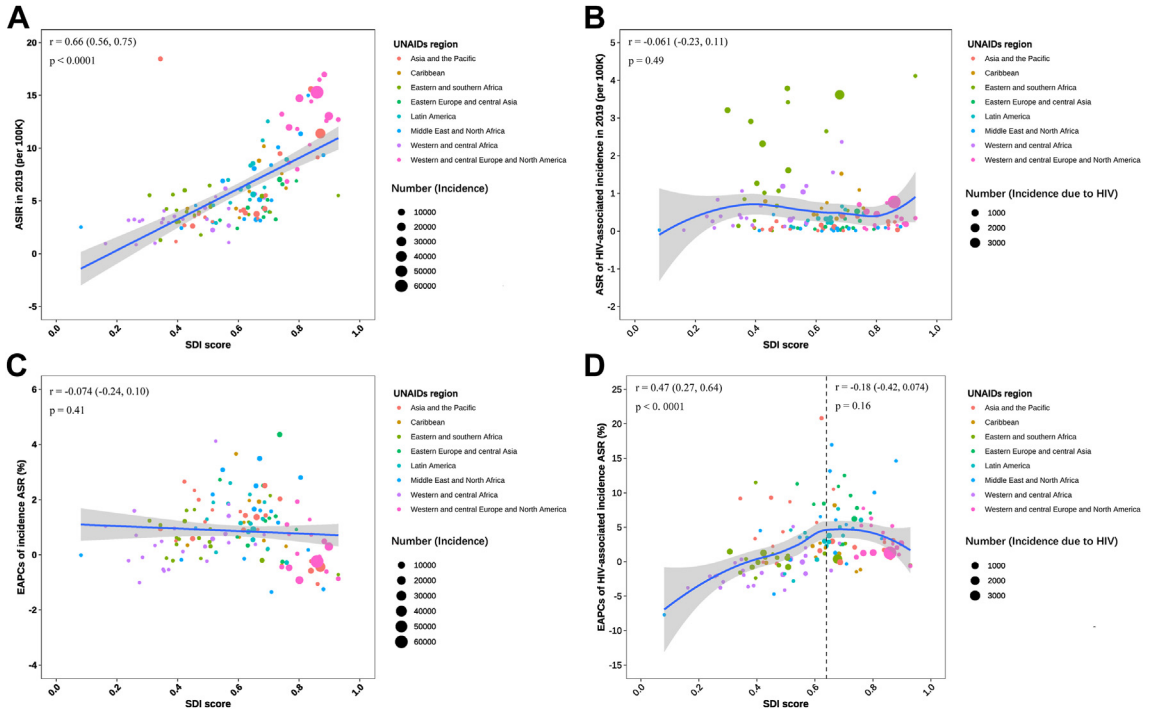

***Fig. 6:* The relationship between ASIR or EAPC of NHL, and SDI**. A, the relationship between the all-cause ASIR and SDI in 2019; B, the relationship between the HIV-associated ASIR and SDI in 2019; C, the relationship between the EAPC of all-cause ASIR from 2010 to 2019 and SDI; D, the relationship between the EAPC of HIV-associated ASIR from 2010 to 2019 and SDI. The colours of the dots correspond to eight UNAIDS-defined regions. The size of the circle is increased with all-cause incidence numbers and HIV-associated incidence numbers in 2019, respectively. ASIR, age-standardised incidence rate; EAPC, estimated annual percentage change; NHL, non-Hodgkin lymphoma; SDI, socio-demographic index.

had a 48% increase in new HIV infections since 2010, becoming the fastest-growing HIV epidemic in the world.[60] Socioeconomic factors, including the legality of drugs and the prevalence of sex workers in some countries of this region also exacerbate the phenomenon in some extent.[61] Additionally, low ART coverage, at only 51%, in this region compared to the Western and central Europe and North America (85%),[51] leads to falling far short of the '90-90-90' UNAIDS target of 86% of HIV-positive individuals on antiretroviral therapy.[13] Therefore, this coverage gap in ART accessibility likely contributes to the higher incidence of NHL in lower-income countries.

In this study, as we used the PAF formula to estimate the proportion attributed to HIV in NHL patients, we need to consider several principles. Firstly, in our study, HIV infection is preventable, so HIV exposure is an eliminable risk factor. Secondly, we used adjusted effect values in PAF calculation (for some studies where adjusted effect values were not reported, we obtained them through external adjustments), but it is important to note that there may still be factors that were not completely adjusted for. Thirdly, HIV exposure is relatively an independent risk factor, but we should also consider the co-infection of HIV with other viruses such as EBV and HTLV-1. Fourthly, we conducted a comprehensive search and included all eligible studies, thoroughly assessed the quality of the literature, extracted and calculated adjusted effect values to minimize selection bias and measurement error to the greatest extent possible.

Meanwhile, this study has certain limitations that may affect the accuracy of the results. First, one limitation is the substantial heterogeneity observed in our meta-analysis. We conducted subgroup and meta-regression analyses to explore potential sources of heterogeneity, and found some characters such as study region, study type, and study period significantly contributed to the heterogeneity. Subsequently, we calculated PAF and HIV-associated NHL incidence based on these subgroup meta-RRs. We incorporated region and time-specific RR values for the calculation of PAF and the burden of HIV-associated NHL at different time periods and regions to ensure better representation. However, ideally the risk estimates should be stratified for PAF calculation by regions within the periods, but we could not accomplish it in this study because of insufficient studies on specific

time intervals across different regions. Second, we incorporated two articles with overlapping populations because their limited overlap and substantial differences in risk ratio values, but we have to acknowledge that this condition could potentially result in bias in the PAF due to the unquantifiable proportion of duplicated populations.[62,63] Third, according to data from the UNAIDS, 55 countries (55/189, 29.1%) have chosen not to disclose their HIV prevalence data, which limits the analysis at the global national level. Fourth, our NHL burden data was derived from the GBD study, which utilizes modelling techniques and incorporates data from varying-quality cancer registries in low- and middle-income countries. Fifth, even though we conducted separate meta-analyses for the risk of different NHL subtypes among patients with HIV, due to the absence of disease burden data for specific NHL subtypes in the GBD 2019 database, we were unable to further calculate the disease burden specifically attributed to HIV for these subtypes. Sixth, because NHL is relatively rare, we ultimately synthesized RR, OR, and SIR values in our meta-analysis. However, even though SIR and RR values are quite similar in this context, we still need to be cautious about the potential heterogeneity between different measures. Seventh, the principle of PAF requires adjustment for all confounding variables in the analysis. Therefore, we used external adjustment methods[26] to obtain all the adjusted effect values for the final meta-analysis and PAF calculation. However, although we externally adjusted unadjusted effect values to obtain adjusted effect values, and ultimately included adjusted effect values in the meta-analysis, not every study adjusted for the same variables, which may introduce unavoidable potential bias. Eighth, due to the limitation of GBD 2019 data, which only extends up to 2019, further updates on the disease burden of HIV-associated NHL beyond 2019 will be necessary in the future. Ninth, in light of limited access to NHL diagnostic and pathology services in some countries, underestimation of NHL incidence may lead to potential limitations. Finally, we only included studies from English databases, which may introduce a certain publication bias.

In summary, our study presents the first global estimates of NHL attributable to HIV infection. We demonstrated a 23-fold higher risk of NHL among PLWH. Addressing this increased risk, we estimated approximately 7% of NHL cases are attributable to HIV infection and the highest is across Eastern and Southern Africa despite the presence of regional disparities despite the presence of regional disparities. Moreover, the global burden of HIV-associated NHL incidence has dramatically increased from 1990 to 2019, with the highest trend in countries within Eastern Europe and Central Asia. These findings underscore the importance of targeted prevention and control policies in countries with high HIV prevalence and limited health services. Policies for stopping the increase of HIV prevalence, including sufficient policies for the management of infectious diseases among migrants, can optimize benefits in these countries hit by HIV. Prioritising these strategies in countries with the highest HIV burden and fastest growing of HIV-associated NHL will contribute substantially to achieving the UNAIDS goal of ending the AIDS epidemic by 2030 and preventing the escalating burden of NHL.

Contributors

YC, JHZ, PS, MLC, YPL, XL, and ZWW designed this analysis and drafted the manuscript. YC, JHZ, YQX, and ZWW finished the data extraction, synthesis, and analysis. PS, ZCS, YLY, YXZ, KNL, and HRH reviewed the results and commented on the manuscript drafts. ZWW and JHZ had full access to the study data and had the final responsibility for the decision to submit the manuscript for publication. ZWW and JHZ have accessed and verified the underlying data. All the authors approved the manuscript.

Data sharing statement

All data in this study were included in this published article and the supplementary information files.

Declaration of interests

All authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102370.

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