BMC Medicine

RESEARCH

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Global, regional and national burden due to retinoblastoma in children aged younger than 10 years from 1990 to 2021

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Abstract

Background Retinoblastoma (RB), an aggressive intraocular malignancy, significantly adds to the global disease burden in early childhood. This study offers insights into the global burden of retinoblastoma (RB) in children aged 0–9 years, examining incidence, mortality, and DALYs from 1990 to 2021, across age, sex, location, and SDI levels. It aims to inform health policy, resource allocation, and RB combat strategies.

Methods Data were retrieved from newly released Global Burden of Disease (GBD) study. The measures were estimated both as numerical counts and age-standardised rates per 100,000 population. Joinpoint regression analysis was used to rigorously examine temporal trends, estimating the average annual percentage change (AAPC). Spearman's correlation test was used to examine the relationship between SDI and the burden of RB by location and year.

Results Globally, the age-standardised incidence rate (ASIR), age-standardised mortality rate (ASMR), and age-standardised DALYs rate (ASDR) for RB among young children in 2021 were 0.09 [95% uncertainty interval (UI): 0.05 to 0.13], 0.04 (95%UI: 0.03 to 0.06), and 3.65 (95%UI: 2.21 to 4.96), respectively. Despite an overall increasing trend in incidence [AAPC: 0.62; 95% confidence interval (CI): 0.42 to 0.82], the RB incidence rate demonstrated a significant decline from 2019 to 2021, while mortality and DALYs rate for RB showed overall downward trends. Trends in ASIR varied across regions, with the highest increase in East Asia. Among all GBD regions, only Southern Sub-Saharan Africa exhibited rising trends in mortality and DALYs rate. Gender comparisons showed negligible differences in ASIR, ASMR and ASDR in 2021. Moreover, the highest disease burden was noted in early neonatal (0–6 days), and in children aged 2–4 years at both global and regional levels. Analysis by SDI indicated that RB incidence rates increased with higher SDI levels. In addition, a significantly negative correlation was found between SDI level and both ASMR and ASDR of RB among children aged 0–9 years.

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Conclusions From 1990 to 2021, RB-related incidence, mortality, and DALYs varied by age and location. Evaluating spatiotemporal trends underscores the impact of health policies and substantial public health interventions on RB control.

Keywords Retinoblastoma, Children, Global burden of disease, Incidence, Mortality, Disability-adjusted life years

Background

Retinoblastoma (RB) is the most common malignant tumor of childhood, with an incidence rate of 1/15,000 to 1/20,000, affecting approximately 8,000 children worldwide each year [1]. Globally, RB accounts for about 6% of all cancers incidence in children under 5 years of age [2, 3]. Moreover, the incidence of RB varies substantially across populations, with up to 50-fold difference between regions. Recent study indicate that the incidence of RB is highest in Africa and Asia [4]. Within Asia, Jordan shows the highest incidence, while India leads in the Asia–Pacific region, closely followed by China [5]. Whilst prior research has suggested a higher incidence in females, the scientific community has yet to reach a consensus on the influence of sex on disease incidence [6]. The mortality from RB is estimated to be below 5% in high-income countries, while it can reach as high as 70% in African countries [7]. Evidence from the Surveillance, Epidemiology, and End Results (SEER) database has indicated a decline in both five- and ten-year relative survival rates of RB in the United States from 2000 to 2018 [8]. This trend may be partially attributed to the highly localized therapies applied in advanced stages of the disease; however, pinpointing the exact factors driving this unanticipated decline in survival rates remains challenging. These findings underscore the importance of maintaining vigilant surveillance on this disease. Epidemiological data are crucial for implementing effective disease prevention measures and informing medical resource allocation to address this substantial but under-examined child health challenge. However, a comprehensive epidemiological profile of RB, especially concerning disease burden metrics like disability-adjusted life years (DALYs) and its spatio-temporal distribution, remains lacking.

The Global Burden of Disease (GBD) dataset is regarded as the largest and most comprehensive study undertaken to present a broad view of health loss from hundreds of diseases, injuries, and risk factors. It provides a unique platform to compare the magnitude of diseases, injuries, and risk factors across different age groups, sexes, locations, and timeframes. Recently, GBD 2021 estimates have been produced, offering updated estimates for the incidence, prevalence, mortality and burden of 371 diseases and injuries across 204 countries and territories and 811 subnational locations from 1990 to 2021 [9–11].

Utilizing the most recent data from GBD 2021, this study provides an all-encompassing evaluation of the global incidence, mortality, and DALYs of RB from 1990 to 2021. The intention behind these findings is to furnish indispensable information to government and healthcare policymakers, allowing them to discern priority sectors for the prevention and control of RB. This, in turn, will support the development of more effective policies and the reasonable distribution of resources.

Methods

Study population and data collection

This prospective study used data from the GBD 2021, accessed via the Global Health Data Exchange (GHDx) results tool, which employed a consistent and comparable approach to extensively assess the population, fertility, disease prevalence, and mortality across 204 countries and territories. Detailed methods are presented in the appendix of the GBD 2021 capstone papers [10, 11]. Briefly, GBD 2021 synthesises a large and growing number of data input sources, including surveys, censuses, vital statistics, and other health-related data sources. These inputs are used to estimate morbidity, illness, injury, and attributable risk across 204 countries and territories from 1990 to 2021, with mortality estimates covering 1980 to 2021. The input sources are accessible through an interactive citation tool in the GHDx, which allows users to view and access records for input sources, export a CSV file that includes metadata, citations, and usage information for specific GBD components, causes, risks, and locations (https://ghdx.healthdata.org/gbd-2021). As required by GATHER, additional metadata for input sources are also available through this citation tool. Data on the incidence, mortality, and DALYs of RB were extracted from the GBD 2021.

The study population was defined as younger children aged 0–9 years, because GBD 2021 only provided the most recent burden estimates for RB among these populations. Furthermore, the 0–9 age range was divided into seven GBD age groups: 0–6 days, 7–27 days, 1–5 months, 6–11 months, 12–23 months, 2–4 years, and 5–9 years.

Definition

According to GBD 2021, RB is defined by the International Statistical Classification of Diseases (ICD), Tenth

Revision (ICD-10), with codes C69.2-C69.22, and by ICD-9 with code 190.5. The Sociodemographic Index (SDI) is a composite indicator representing the social and economic conditions that influence health outcomes in each location. In short, it is the geometric mean of 0 to 1 indices of total fertility rate among those younger than 25 years old, mean educational attainment for those aged 15 and older, and lag-distributed income per capita. The detailed explanation of the SDI was presented in Additional file 1: Supplementary methods.

In current study, years lived with disability (YLDs) were calculated by multiplying the prevalence of RB at varying severity levels by corresponding disability weights. Additionally, years of life lost (YLLs) were computed by multiplying the number of deaths in each age bracket by the remaining life expectancy for that age group. The DALYs is a summary measure that quantifies the overall burden of disease, which was the sum of YLLs and YLDs. One DALYs can be regarded as the loss of 1 year in total health. The detailed estimates on RB related incidence, mortality and DALYs were presented in Additional file 1: Supplementary methods. All the above measures were presented as counts and rates per 100,000 population. The 95% uncertainty interval (UI) was derived by using the 2.5th and 97.5th percentiles of an ordered set of 1000 draws. Age-standardised populations were calculated using the GBD world population age standard.

Data analysis

In the present study, we described the number and age-standardised rate of incidence, mortality, and DALYs for RB by age, sex, and location. Moreover, we employed the Joinpoint regression analysis model, a statistical methodology widely used in epidemiological studies, to examine temporal changes in disease prevalence and mortality. This model expertly identifies and quantitatively describes significant turning points in the time-series data related to the estimate of RB at global, regional, and national levels. The model facilitated the determination of the annual percent change (APC) and its corresponding 95% confidence interval (CI) to outline trends for the indicators over defined time periods. Additionally, for a comprehensive evaluation of the observed trends, the average annual percent change (AAPC) was also computed, which consolidated trend data over the study duration from 1990 to 2021. Statistically, an APC or AAPC estimate, with its 95% CI lower limit surpassing zero, indicates an increasing trend within the specified interval. Conversely, an estimate with a 95% CI upper limit less than zero indicates a decreasing trend. If the 95% CI for the APC or AAPC includes zero, it suggests that the trend has remained stable. Finally, Spearman's correlation test was used to evaluate the association between SDI with the burden of RB by location and year. A significance level was set at a p-value less than 0.05. All analyses were performed using R software (version 4.2.2).

Ethical considerations

This study used publicly available data from the GBD study, which is ethically approved by the Institutional Review Board at the University of Washington. No personal identifiable information was used in the analysis.

Role of the funding source

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

Results

Global level

In 2021, the global incidence of RB was estimated at 6274.97 cases (95% UI: 3854.96 to 8381.78), an increase from 4673.52 cases (95% UI: 3033.33 to 5953.1) in 1990, reflecting a 34% increase (95% UI: 5.00% to 64.00%) from 1990 to 2021 (Table 1). Additionally, the global age-standardised incidence rate (ASIR) of RB rose from 0.08 per 100,000 population (95% UI: 0.05 to 0.10) in 1990 to 0.09 per 100,000 population (95% UI: 0.06 to 0.13) in 2021, with an AAPC of 0.62 (95% CI: 0.42 to 0.82) during this period (Table 1). The number of deaths due to RB was 2762.04 (95% UI: 1666.28 to 3760.79) in 2021, with an age-standardised mortality rate (ASMR) of 0.04 per 100,000 population (95% UI: 0.03 to 0.06), showing a decrease trend with AAPC of -0.70 (95% CI: -0.87 to -0.53) from 1990 to 2021 (Table 1). Furthermore, the global DALYs for RB in 2021 was 243204.27 (95% UI: 147357.66 to 330473.92), with an age-standardised DALYs rate (ASDR) of 3.65 per 100,000 population (95% UI: 2.21 to 4.96), which showed with downward trend with an AAPC of -0.69 (95% CI: -0.86 to -0.52) between 1990 and 2021 (Table 1).

Joinpoint regression analyses showed an increasing trend in the incidence of RB among children younger than 10 years old from 1990 to 2019, but followed by a significant decrease between 2019 and 2021 [APC: -8.89, $P<0.05$]. As shown in Additional file 2: Fig. S1, the ASMR of RB decreased slowly from 1990 to 2002, followed by two significant rapid declines from 2014 to 2019 (APC = -1.94, $P<0.05$) and from 2019 to 2021 (APC = -3.58, $P<0.05$). A similar trend was observed in the ASDR, with the most notable decrease occurring from 2019 to 2021 (APC = -3.72, $P<0.05$) (Additional file 2: Table S1).

Table 1 Incidence, deaths and DALYs of retinoblastoma in children aged younger than 10 years in 1990 and 2021, and change from 1990 to 2021

	Number, (95% UI)		1990–2021 Percentage change (95% UI)	ASR, per 100,000 population (95% UI)		AAPC (95% CI)
	1990	2021		1990	2021	
By sex groups						
Both sexes						
Incidence	4673.52 (3033.33 to 5953.1)	6274.97 (3854.96 to 8381.78)	0.34 (0.05 to 0.64)	0.08 (0.05 to 0.10)	0.09 (0.05 to 0.13)	0.62 (0.42 to 0.82)
Deaths	3179.83 (1819.02 to 4172.8)	2762.04 (1666.28 to 3760.79)	-0.13 (-0.34 to 0.14)	0.05 (0.03 to 0.07)	0.04 (0.03 to 0.06)	-0.70 (-0.87 to -0.53)
DALYs	279066.14 (159656.45 to 365149.79)	125385.75 (65266.11 to 180824.51)	-0.13 (-0.34 to 0.14)	4.54 (2.60 to 5.94)	3.65 (2.21 to 4.96)	-0.69 (-0.86 to -0.52)
Boys						
Incidence	2410.74 (1435.95 to 3243.18)	3252.15 (1846.39 to 4461.52)	0.35 (0.02 to 0.75)	0.08 (0.05 to 0.10)	0.09 (0.05 to 0.13)	0.64 (0.51 to 0.76)
Deaths	1650.42 (810.15 to 2308.05)	1424.66 (739.58 to 2057.8)	-0.14 (-0.4 to 0.23)	0.05 (0.03 to 0.07)	0.04 (0.02 to 0.06)	-0.73 (-0.86 to -0.60)
DALYs	144682.66 (71222.75 to 202318.81)	117818.52 (55125.56 to 168087.88)	-0.13 (-0.4 to 0.23)	4.57 (2.25 to 6.39)	3.64 (1.90 to 5.26)	-0.72 (-0.84 to -0.59)
Girls						
Incidence	2262.78 (1270.54 to 3052.55)	3022.82 (1487.72 to 4248.09)	0.34 (0.02 to 0.66)	0.08 (0.04 to 0.10)	0.09 (0.06 to 0.13)	0.67 (0.46 to 0.88)
Deaths	1529.4 (656.66 to 2123.4)	1337.38 (623.07 to 1913.08)	-0.13 (-0.34 to 0.12)	0.05 (0.02 to 0.07)	0.04 (0.02 to 0.06)	-0.68 (-0.85 to -0.51)
DALYs	134383.48 (57787.02 to 186200.84)	243204.27 (147357.66 to 330473.92)	-0.12 (-0.33 to 0.13)	4.51 (1.94 to 6.25)	3.67 (1.72 to 5.22)	-0.67 (-0.84 to -0.50)
By age groups						
0–6 days						
Incidence	23.06 (15.33 to 30.17)	25.04 (15.34 to 34.53)	0.09 (-0.14 to 0.37)	0.91 (0.6 to 1.19)	1.02 (0.63 to 1.41)	0.41 (0.14 to 0.67)
Deaths	15.61 (8.88 to 20.97)	10.49 (5.68 to 14.68)	-0.33 (-0.49 to -0.12)	0.61 (0.35 to 0.83)	0.43 (0.23 to 0.60)	-1.17 (-1.28 to -1.06)
DALYs	1418.01 (808.18 to 1905.77)	957.75 (521 to 1336.61)	-0.32 (-0.49 to -0.11)	55.85 (31.83 to 75.06)	39.07 (21.25 to 54.53)	-1.15 (-1.26 to -1.04)
7–27 days						
Incidence	8.8 (6.34 to 11.47)	12.08 (8.39 to 16.25)	0.37 (0.08 to 0.71)	0.12 (0.08 to 0.15)	0.17 (0.12 to 0.22)	1.18 (0.64 to 1.72)
Deaths	5.28 (3.26 to 6.99)	3.41 (2.03 to 4.74)	-0.35 (-0.5 to -0.15)	0.07 (0.04 to 0.09)	0.05 (0.03 to 0.06)	-1.33 (-1.61 to -1.04)
DALYs	480.36 (296.95 to 635.44)	314.07 (187.7 to 435.01)	-0.35 (-0.5 to -0.14)	6.4 (3.96 to 8.47)	4.31 (2.57 to 5.96)	-1.32 (-1.54 to -1.10)
1–5 months						
Incidence	231.07 (134.43 to 312.56)	296.98 (178.25 to 409.91)	0.29 (-0.07 to 0.69)	0.42 (0.25 to 0.57)	0.55 (0.33 to 0.76)	0.88 (0.68 to 1.09)
Deaths	170.01 (86.15 to 242.59)	131.12 (74.33 to 183.28)	-0.23 (-0.48 to 0.05)	0.31 (0.16 to 0.44)	0.24 (0.14 to 0.34)	-0.83 (-1.02 to -0.64)
DALYs	15393.24 (7802.02 to 21955.64)	11939.99 (6781.94 to 16641.38)	-0.22 (-0.47 to 0.05)	28.19 (14.29 to 40.21)	22.21 (12.62 to 30.96)	-0.81 (-1.00 to -0.63)
6–11 months						
Incidence	278.59 (149.26 to 389.08)	368.96 (201.51 to 535.63)	0.32 (-0.11 to 0.87)	0.44 (0.24 to 0.62)	0.58 (0.32 to 0.85)	0.97 (0.63 to 1.31)
Deaths	218.91 (102.9 to 319.8)	206.75 (110.5 to 320.65)	-0.06 (-0.39 to 0.41)	0.35 (0.16 to 0.51)	0.33 (0.17 to 0.51)	-0.19 (-0.34 to -0.04)
DALYs	19712.3 (9289.83 to 28738.34)	18679.1 (9982.31 to 28941.33)	-0.05 (-0.39 to 0.41)	31.23 (14.72 to 45.54)	29.56 (15.8 to 45.8)	-0.19 (-0.34 to -0.04)
12–23 months						
Incidence	645.31 (438.94 to 834.22)	1025.57 (567.3 to 1431.33)	0.59 (0.16 to 1.17)	0.52 (0.35 to 0.67)	0.80 (0.44 to 1.11)	1.37 (1.06 to 1.67)

Table 1 (continued)

	Number, (95% UI)		1990–2021 Percentage change (95% UI)	ASR, per 100,000 population (95% UI)		AAPC (95% CI)
	1990	2021		1990	2021	
Deaths	365.18 (207.56 to 488.87)	306.37 (175.64 to 426.52)	-0.16 (-0.37 to 0.12)	0.29 (0.17 to 0.39)	0.24 (0.14 to 0.33)	-0.66 (-0.76 to -0.56)
DALYs	32718.9 (18659.3 to 43657.83)	27727.51 (15953.59 to 38599.01)	-0.15 (-0.37 to 0.13)	26.26 (14.97 to 35.03)	21.59 (12.42 to 30.06)	-0.63 (-0.74 to -0.52)
2–4 years						
Incidence	2836.22 (1789.75 to 3719.09)	3649.43 (2169.18 to 5110.76)	0.29 (-0.03 to 0.64)	0.77 (0.49 to 1.01)	0.91 (0.54 to 1.27)	0.42 (0.26 to 0.58)
Deaths	2027.79 (1150.11 to 2694.44)	1781.16 (1068.08 to 2501.36)	-0.12 (-0.36 to 0.19)	0.55 (0.31 to 0.73)	0.44 (0.26 to 0.62)	-0.72 (-0.92 to -0.52)
DALYs	177718.26 (101267.82 to 236068.53)	156337 (93921.64 to 219378.25)	-0.12 (-0.36 to 0.19)	48.35 (27.55 to 64.22)	38.79 (23.3 to 54.43)	-0.72 (-0.92 to -0.52)
5–9 years						
Incidence	650.46 (444.37 to 842.39)	896.91 (573.03 to 1233.99)	0.38 (0.1 to 0.68)	0.11 (0.08 to 0.14)	0.13 (0.08 to 0.18)	0.54 (0.02 to 1.07)
Deaths	377.04 (214.99 to 514.5)	322.74 (189.68 to 426.58)	-0.14 (-0.35 to 0.07)	0.06 (0.04 to 0.09)	0.05 (0.03 to 0.06)	-0.97 (-1.22 to -0.71)
DALYs	31625.07 (18113.11 to 43127.48)	27248.84 (16117.81 to 35912.42)	-0.14 (-0.35 to 0.08)	5.42 (3.1 to 7.39)	3.97 (2.35 to 5.23)	-0.95 (-1.20 to -0.70)

AAPC average annual percent change, *ASR* age-standardised rate, *CI* confidence interval, *DALYs* Disability-Adjusted Life Years, *UI* uncertainty interval

Regional level

In 2021, the highest ASIR of RB was observed in high-middle SDI regions at 0.13 per 100,000 population (95% UI: 0.07 to 0.19) (Additional file 2: Table S2). Geographically, Eastern Sub-Saharan Africa had the highest ASIR, at 0.20 per 100,000 population (95% UI: 0.12 to 0.31), followed by Andean Latin America at 0.18 per 100,000 population (95% UI: 0.10 to 0.30), and Western Europe at 0.17 per 100,000 population (95% UI: 0.12 to 0.21). Interestingly, relatively high-income regions demonstrated obviously lower ASIRs, including Caribbean at 0.01 per 100,000 population (95% UI: 0.01 to 0.02), Oceania at 0.02 per 100,000 population (95% UI: 0.01 to 0.05), and Australasia at 0.02 per 100,000 population (95% UI: 0.01 to 0.03) (Additional file 2: Table S2). From 1990 to 2021, ASIR trends varied across regions, with a significant increase observed in high-middle SDI regions (AAPC: 2.08, 95% CI: 1.29 to 2.87), while low SDI regions experienced the largest decline (AAPC: -0.73, 95% CI: -0.86 to -0.60). High SDI regions, in contrast, showed stable ASIR trends (AAPC: -0.26, 95% CI: -0.78 to 0.26) (Additional file 2: Table S2). Geographically, East Asia showed the highest increase (AAPC: 3.16, 95% CI: 2.53 to 3.79), whereas Australasia exhibited the most significant decline (AAPC: -3.52, 95% CI: -6.26 to -0.69), followed by Caribbean (AAPC: -3.25, 95% CI: -5.26 to -1.19), and High-income North America (AAPC: -2.06, 95% CI: -3.12 to -0.98) (Additional file 2: Table S2).

The highest ASMR of RB in 2021 was found in low SDI regions, at 0.09 per 100,000 population (95% UI: 0.05 to 0.13), while the lowest ASMR was recorded in high SDI regions. The most significant ASMR decrease was observed in high SDI regions (AAPC: -3.44, 95% CI: -4.24 to -2.63) (Additional file 2: Table S2). Geographically, Eastern Sub-Saharan Africa had the highest ASMR, at 0.17 per 100,000 population (95% UI: 0.11 to 0.26), followed by Western sub-Saharan Africa at 0.08 per 100,000 population (95% UI: 0.03 to 0.12), and Southern Sub-Saharan Africa at 0.04 per 100,000 population (95% UI: 0.02 to 0.07) (Additional file 2: Table S2). It is noteworthy that, from 1990 to 2021, the Southern Sub-Saharan Africa experienced the most significant increase in ASMR (AAPC: 0.98, 95% CI: 0.40 to 1.57), while other regions exhibited downward trends, with Australasia (AAPC: -6.95, 95% CI: -9.34 to -4.50), Southern Latin America (AAPC: -5.02, 95% CI: -6.10 to -3.93), and Central Europe (AAPC: -4.16, 95% CI: -5.54 to -2.76) showing the most pronounced declines (Additional file 2: Table S2).

The burden of RB, as measured by ASDR, was highest in low SDI regions, reaching 7.80 per 100,000 population (95% UI: 4.70 to 11.24) in 2021. High SDI regions, conversely, showed the lowest ASDR of RB at 0.26 per 100,000 population (95% UI: 0.20 to 0.32). Geographically, Eastern Sub-Saharan Africa recorded the highest ASDR, at 14.67 per 100,000 population (95% UI: 9.70 to 22.54), followed by Western sub-Saharan Africa at 6.69 per 100,000 population (95% UI: 2.81 to 10.58), and

Andean Latin America at 3.73 per 100,000 population (95% UI: 2.31 to 6.08) (Additional file 2: Table S2). Of note, almost all regions showed downward trends in disease burden from 1990 to 2021, with Australasia (AAPC: -6.00, 95% CI: -9.21 to -2.68), Southern Latin America (AAPC: -4.78, 95% CI: -5.84 to -3.71), and Central Europe (AAPC: -3.93, 95% CI: -5.31 to -2.53) showing the most notable reductions. The only region with a significant upward ASDR trend was Southern Sub-Saharan Africa (AAPC: 1.00, 95% CI: 0.42 to 1.58) (Additional file 2: Table S2).

National level

The country-specific distribution of ASIR for RB is detailed in Additional file 2: Fig. 1 and Table S3. Notably, in 2021, Tokelau (1.19 per 100,000 population; 95% UI: 0.25 to 3.86), Kenya (0.51 per 100,000 population; 95% UI: 0.27 to 0.83), Malawi (0.44 per 100,000 population; 95% UI: 0.17 to 0.89), Portugal (0.44 per 100,000 population; 95% UI: 0.30 to 0.54), and Finland (0.37 per 100,000 population; 95% UI: 0.23 to 0.51) showed the highest ASIR (Fig. 1D and Additional file 2: Table S3). From 1990 to 2021, changes in ASIR varied across countries, with the most substantial relative increases observed in Tokelau (AAPC: 19.13, 95% CI: 14.98 to 23.42), Armenia (AAPC: 13.08, 95% CI: 12.32 to 13.84), and Cook Islands (AAPC: 9.34, 95% CI: 8.18 to 10.51) (Additional file 2: Table S3). Conversely, Cuba (AAPC: -8.30, 95% CI: -12.69 to -3.67), Kuwait (AAPC: -8.29, 95% CI: -10.52 to -6.00), and Lithuania (AAPC: -7.89, 95% CI: -9.39 to -6.36) experienced the largest decreases in ASIR of RB.

In 2021, Malawi (0.40 per 100,000 population; 95% UI: 0.16 to 0.88), Tokelau (0.37 per 100,000 population; 95% UI: 0.08 to 1.23), and Kenya (0.36 per 100,000 population; 95% UI: 0.20 to 0.57) recorded the highest ASMR (Fig. 1E and Additional file 2: Table S3). From 1990 to 2021, Tokelau (AAPC: 15.27, 95% CI: 11.06 to 19.64), Armenia (AAPC: 9.61, 95% CI: 8.52 to 10.71), and Georgia (AAPC: 7.30, 95% CI: 4.89 to 9.77) showed the largest increases in ASMR (Additional file 2: Table S3). Conversely, Kuwait (AAPC: -10.80, 95% CI: -12.91 to -8.64), Cuba (AAPC: -10.64, 95% CI: -15.20 to -5.83), and Lithuania (AAPC: -10.22, 95% CI: -11.63 to -8.80) had the most significant decreases in ASMR (Additional file 2: Table S3). A Similar pattern was found in terms of DALYs.

By age and gender patterns

Our findings indicate that while the incidence and mortality cases of RB were higher in boys than in girls, the ASIR and ASMR as well as ASDR were comparable between genders both in 1990 and 2021 (Table 1). From 1990 to 2021, the ASIR for RB increased in both boys and girls, with an AAPC of 0.64 (95% CI: 0.51 to 0.76) in boys, and 0.67 (95% CI: 0.46 to 0.88) in girls. Mortality numbers were slightly higher in boys, while the DALYs were lower compared to girls in 2021. Moreover, both ASMR and ASDR declined from 1990 to 2021 for both genders. The AAPC of ASMR was -0.73 (95% CI: -0.86 to -0.60) in boys, and -0.68 (95%CI:

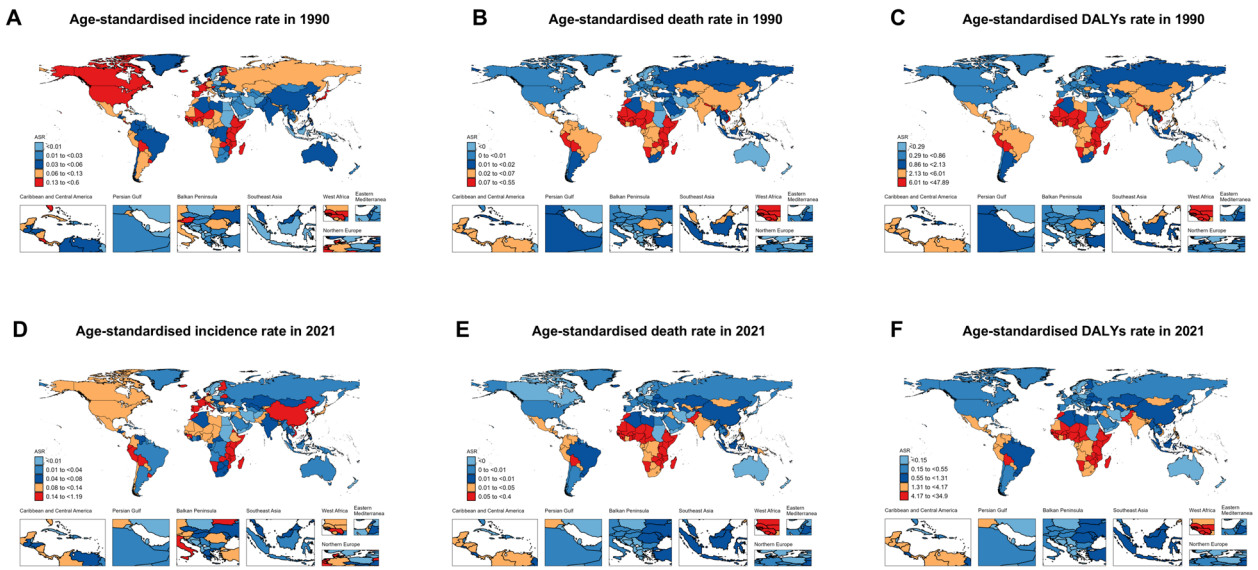

Fig. 1 Age-standardised rates of incidence, deaths, and DALYs of retinoblastoma in children aged younger than 10 years in 1990 and 2021 among 204 countries and territories. **A** Age-standardised incidence rate in 1990; **B** Age-standardised death rate in 1990; **C** Age-standardised DALYs rate in 1990; **D** Age-standardised incidence rate in 2021; **E** Age-standardised death rate in 2021; **F** Age-standardised DALYs rate in 2021. DALYs, disability-adjusted life years

-0.85 to -0.51) in girls. Similarly, the AAPC of ASDR was -0.72 (95% CI: -0.84 to -0.59) for boys, and -0.67 (95% CI: -0.84 to -0.50) for girls (Table 1). Regionally, the most significant disparities in incidence, mortality, and DALYs rates between genders were observed in high income Asia pacific, and Southern Sub-Saharan Africa (Fig. 2).

In terms of age, the highest RB incidence in 2021 was observed in infants younger than 6 days, at 1.02 per 100,000 population (95%UI: 0.63 to 1.41), followed by children aged 2–4 years (0.91 per 100,000 population; 95%UI: 0.54 to 1.27), and 12–23 months old (0.80 per 100,000 population; 95%UI: 0.44 to 1.11) (Table 1, Fig. 3).

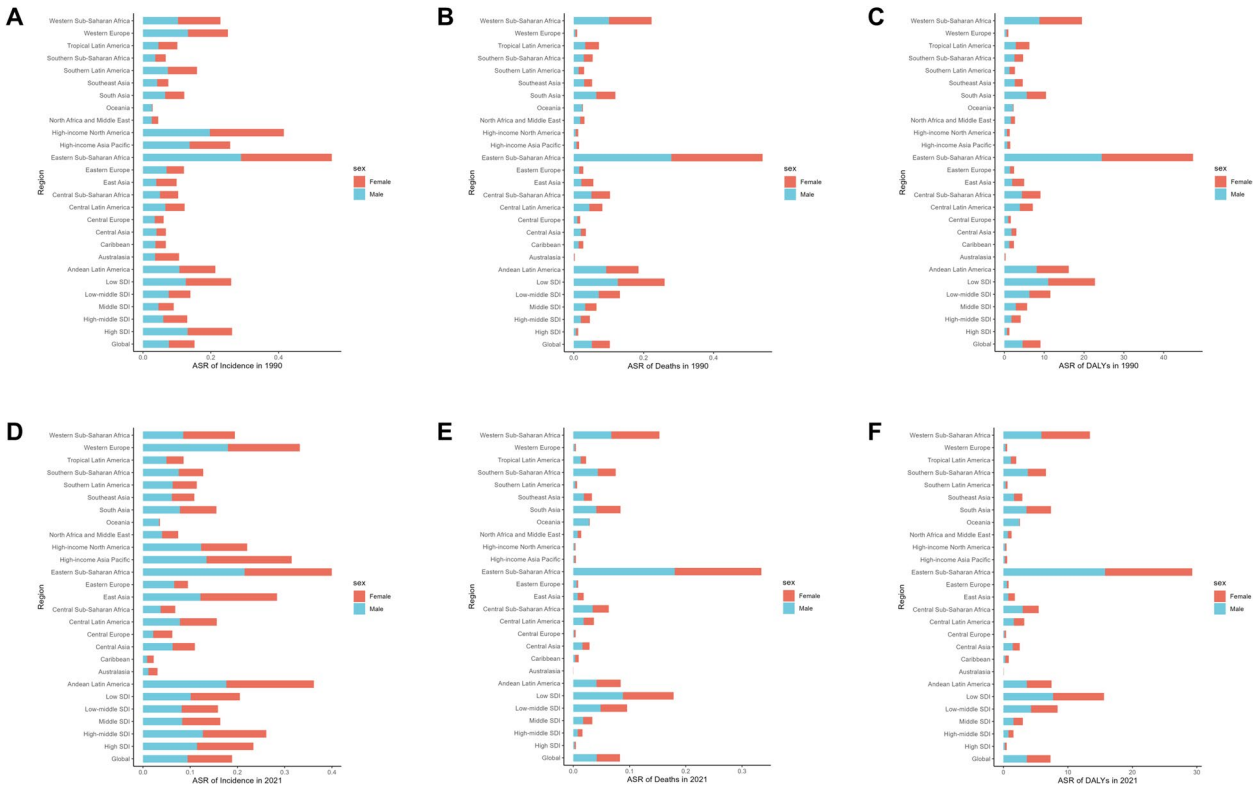

Fig. 2 Age-standardised rates of incidence, deaths, and DALYs of retinoblastoma in children aged younger than 10 years in 1990 and 2021, by sex and region. **A** Age-standardised incidence rate in 1990; **B** Age-standardised death rate in 1990; **C** Age-standardised DALYs rate in 1990; **D** Age-standardised incidence rate in 2021; **E** Age-standardised death rate in 2021; **F** Age-standardised DALYs rate in 2021

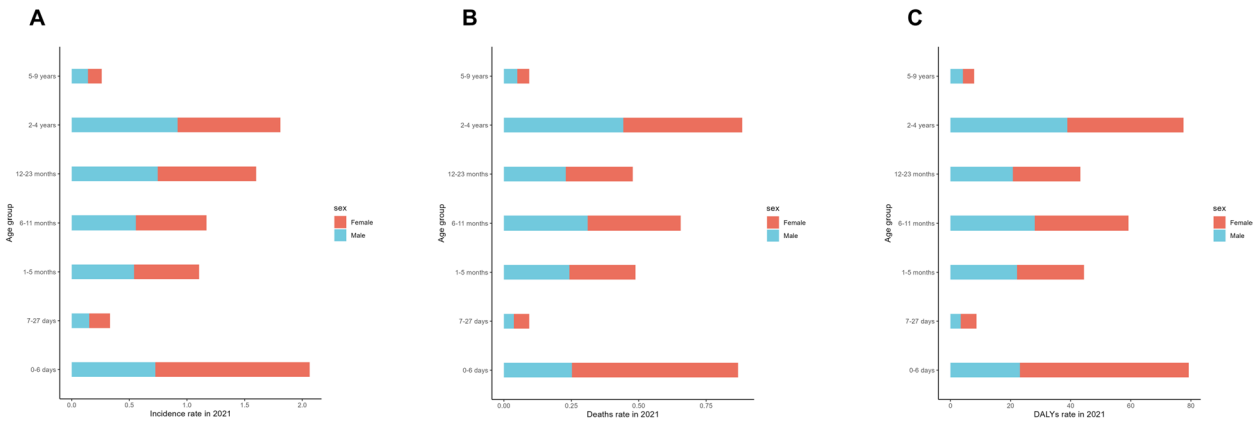

Fig. 3 Global incidence, deaths, and DALYs rate of retinoblastoma in children aged younger than 10 years in 2021, by sex and age subgroups. **A** Incidence rate in 2021; **B** Death rate in 2021; **C** DALYs rate in 2021

However, the lowest incidence occured in children aged 5–9 years, at 0.13 per 100,000 population (95%UI: 0.08 to 0.18). All seven age groups showed increased incidence rates for RB over the study period, with the largest increase observed in children aged 12–23 months (AAPC: 1.37, 95% CI: 1.06 to 1.67). The description of incidence, mortality, and DALYs rate of RB by age at different SDI levels were shown in Fig. 4. In 2021, the mortality rate was highest in the 2–4 years age group (0.44 per 100,000 population; 95%UI: 0.26 to 0.62), followed by 0–6 days group (0.43 per 100,000 population; 95%UI: 0.23 to 0.60), with the lowest mortality rate observed in the 7–27 days and 5–9 years age group (Table 1). All age groups showed downward trends in mortality rates from 1990 to 2021, with the largest decline in children aged 7–27 days (AAPC: -1.33, 95%CI: -1.61 to -1.04). The DALYs rate followed a similar trend, with decreases across all age groups (Table 1). Globally, the largest disparities in incidence, mortality, and DALYs rates between genders were observed among 0–6 days group (Fig. 3).

By SDI

Spearman rank order correlation analyses showed a positive correlation between SDI level and ASIR of RB in children aged 0–9 years ($r=0.154$, $P<0.01$; Additional file 2: Fig. S2A). In term of mortality, a significant negative correlation was observed between SDI level and ASMR ($r=$-0.669, $P<0.01$; Additional file 2: Fig. S3A). Additionally, the ASDR of RB was inversely associated with SDI level ($r=$-0.665, $P<0.01$; Additional file 2: Fig. S4A). Among the 204 countries and territories, there was no significant association between the SDI and ASIR of RB ($r=$-0.021, $P=0.77$). Tokelau and Kenya were significantly higher than expected (Additional file 2: Fig. S2). Consistent with the association between mortality and SDI ($r=$-0.535, $P<0.01$), a marked inverse correlation was also observed between DALYs and SDI ($r=$-0.531, $P<0.01$) (Figures S3 and S4).

Discussion

RB is the most common intraocular tumor in children, accounting for 3% of all pediatric cancers, posing a considerable global public health challenge. While prior research has highlighted the importance of addressing RB in children, the global burden of the disease has remained inadequately quantified. Notably, the present study offers the first-time critical evaluation of the disease burden of RB and introduces an innovative assessment of its temporal trends in children aged 0–9 years, empowering regional governments to implement suitable preventative measures for RB in children. Strengthening prevention and treatment efforts is essential for diminishing the global disease burden of RB in children.

In 2021, the global ASIR for RB has significantly increased compared to 1990, but the overall ASMR and ASDR have shown noticeable declines. According to the World Health Organization (WHO) Guide for Effective Programmes in Cancer Control, programs are recommended for 'early diagnosis' (target children with common symptoms). American Academy of Ophthalmic Oncologists and Pathologists has formulated clear guidelines for detection of RB in children 'at risk' for disease and these are practiced widely [12]. Countries including Canada, Mexico, United Kingdom, Kenya, India, Australia, and New Zealand have adopted 'early diagnosis' projects mainly using red reflex examination for neonates, infants, and children [13], which likely contributed to the rise in new RB cases. RB can be inherited [14], and more than nine out of every ten sufferers surviving into adulthood in developed countries [15, 16], thus, extended

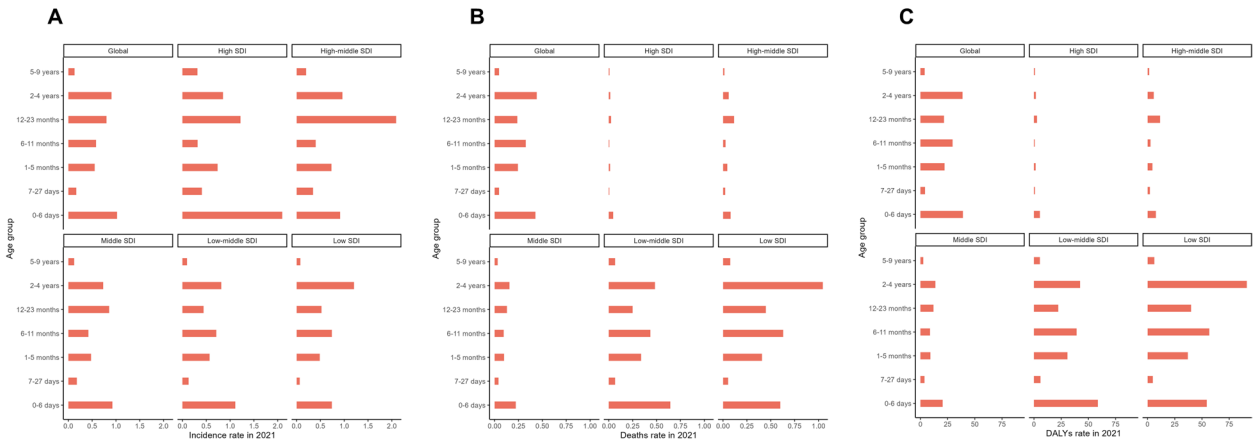

Fig. 4 Global incidence, deaths, and DALYs rate of retinoblastoma in children aged younger than 10 years in 2021, by age and SDI region. **A** Incidence rate in 2021; **B** Death rate in 2021; **C** DALYs rate in 2021

survival of inherited patients may also lead to an increase in morbidity. Besides, improvements in therapeutic and health care were the most important factors contributing to the decrease in deaths and DALYs associated with RB [17]. Interestingly, our Joinpoint regression analysis indicated a significant decline in global ASIR of RB from 2019 to 2021. This shift may reflect enhanced RB management policies introduced by global health organizations and governments around 2019 [18]. Enhancing awareness among healthcare professionals along with incorporating data from refugee populations are vital steps towards advancing our understanding of disease epidemiology [19]. In addition, the emergence of the COVID-19 pandemic in late 2019 and early 2020 has influenced the implementation of prevention and treatment strategies for RB, potentially impacting short-term epidemiological trends in RB incidence [20–23]. Moreover, evolving treatment methods, particularly the shift away from external beam radiation therapy (EBRT), have profoundly influenced the long-term health of RB survivors. EBRT has been associated with an increased risk of second malignant neoplasms, significantly contributing to lifelong DALYs [24–26]. As our study spans from 1990 to 2021, it is important to note that many children diagnosed and treated in the early 1990s may have received EBRT, potentially skewing the long-term health outcomes compared to those diagnosed after 2000, when treatment protocols began to favor less harmful alternatives [27]. However, we do not have specific evidence to support this hypothesis, and further research is needed to confirm these trends and their implications.

We noticed that high SDI regions had higher incidence but lower mortality and burden from RB. This may result from the more common high-energy activities in high SDI regions. Generally, high SDI regions also have better medical education and doctor training, which could offer better medical services to reduce burden. Moreover, social relationships and social status are also powerful determinants of individual health, and high SDI regions could provide more social support and welfare, contributing to better recovery. The welfare and social policies in high SDI regions could, to a great extent, diminish the considerable financial gap between people with and without disability. On the contrary, the higher mortality and burden in low-SDI regions may result from the lack of cancer screening system and poor health care conditions.

In our analysis of the global burden of RB, it is essential to consider the influence of genetic predisposition on key outcomes such as mortality and DALYs. RB is primarily driven by genetic factors, with the majority of cases linked to mutations in the RB1 gene [28]. These genetic anomalies can result in heritable forms of the disease, significantly impacting not only incidence rates but also treatment responses and survival outcomes [29]. Research indicates that advancements in genetic knowledge, particularly since the mid-1990s, have improved early detection and intervention strategies in high-income countries [2, 6, 30]. For instance, the ability to identify at-risk families through genetic testing allows for proactive surveillance and timely treatment, contributing to better survival rates. In contrast, low- and middle-income countries (LMICs) may lack access to genetic testing and counseling, leading to delayed diagnoses and poorer outcomes. Moreover, the disparities highlighted in our findings underscore the urgent need for LMICs to integrate genetic knowledge into their healthcare frameworks. This could involve training healthcare providers in genetic counseling and facilitating access to genetic testing, thereby enabling early detection of RB in high-risk populations. Such initiatives are not only vital for improving individual patient outcomes but also align with the WHO's objectives to address inequities in childhood cancer survival.

From 1990 to 2021, despite a rapid rise in the incidence of RB among children aged 0–9 years in East Asia countries including China, South Korea, and North Korea, a decline in mortality and disease burden has been observed. The increasing trend of RB in East Asia can be attributed to several interrelated factors. First, improved detection and diagnosis, driven by heightened awareness among healthcare providers and advancements in diagnostic technologies, likely contribute to a rise in identified cases [31, 32]. Additionally, genetic predispositions specific to certain populations may play a role, as hereditary mutations associated with RB could be more prevalent in East Asia [33]. Environmental influences, such as increased pollution and changing lifestyle factors, may also be linked to rising cancer rates [34, 35]. Furthermore, disparities in healthcare access, particularly between urban and rural areas, may have historically led to underreporting, with recent improvements in access resulting in more cases being diagnosed. Conversely, Southern Sub-Saharan Africa including Namibia, and South Africa emerges as a region warranting heightened attention, with its incidence, mortality, and disease burden escalating worldwide. Notably, this region possesses the second-highest rank of rising global incidence and is the only region where ASMR and ASDR are on an upward trend. This highlights the low SDI region exhibiting an increase in mortality rates and burden of disease. Furthermore, within populous regions characterized by elevated birth rates, such as Asia and Africa, the frequency and repercussions of RB are substantively pronounced, contributing significantly to the worldwide disease burden [15]. Countries demonstrating high RB incidence have also reported the most substantial mortality rates,

with approximately 40 to 70% of affected individuals succumbing to the disease. Comparatively, mortality rates range between 3 to 5% in regions such as Europe, Canada, and the USA [36, 37]. In developing nations, mortality rate remains exceedingly high, accounting for 95% of total cases [38]. This is primarily attributed to delayed intervention resulting from tardy diagnoses. Factors such as impoverishment, lack of understanding or awareness of the disease's ramifications impede timely access to healthcare services [39]. Some countries conducting early diagnosis, e.g., Canada and Australia, showed significant decline trends in incidence, mortality, and DALYs. Although there is higher ASIR in Kenya in 2021, its ASMR and ASDR showed a downward trend from 1990 to 2021. Therefore, implementing an early screening protocol is essential to mitigate the burden caused by RB across both developed and developing countries.

Furthermore, we found a slightly higher incidence and mortality cases in boys compared to girls, though the overall disease burden is lower in boys. There are no significant gender differences in the morbidity, mortality and burden rates of RB. Similarly, a previous review involving 4,351 new RB cases in 2017 suggested that there was no sex predilection associated with RB. However, sex differences existed in specific countries, such as Asia, and India, which may be probably related to gender discrimination [40]. In contrast with our findings, previous retrospective population-based cohort study using the Taiwan National Health Insurance Research Database (1998–2011) indicated that there were more cases in boys than girls [41]. Moreover, the RB incidence rate during 2000–2009 among boys in SEER 18 was significantly higher than that among girls [42]. Following (SEER) data 2000–2017 indicated that increased cumulative incidence and excess mortality of RB was observed among male children, which may be explained in part by male X-linkage [43]. However, there are no updated evidence on the gender disparity of RB based on worldwide population.

To the best of our knowledge, there is few evidence on the detailed epidemiologic characteristics of RB among different age groups. Compared with GBD 2019 grouped younger children into the relatively broad 1–4-year-old category, the GBD 2021 update further disaggregated age groups under 5 years into more specific categories: 0–6 days, 7–27 days, 1–5 months, 6–11 months, 12–23 months, and 2–4 years. Globally, we found higher morbidity, mortality and disease burden in both early neonatal age (0–6 days) and children aged 2–4 years compared with other age groups. This may support tailored recommendations, as healthcare needs and caregiver demands can differ significantly within these distinct age groups. Recently, another research team provides valuable insights into the retinoblastoma burden in children under 4 years of age [44]. However, our current research broadens this perspective to include children under 10 years, thereby encompassing a broader segment of the pediatric population affected by retinoblastoma. Additionally, our research introduces a more sophisticated categorization method by leveraging the five SDI regions as outlined in the GBD Study 2021 criteria including low, low-middle, middle, high-middle, and high SDI regions. This refined approach facilitates a more granular analysis of the retinoblastoma burden across diverse socio-economic strata, offering a contrast to the four income groupings (high income, upper-middle income, lower-middle income, and low income) utilized in the previously mentioned study. Therefore, our study provides a more detailed and contextualized view of the retinoblastoma burden, which is essential for the development of targeted interventions and health policies worldwide.

RB continues to pose a significant health challenge for low- and middle-income countries. However, high SDI regions also exhibited a relative higher incidence of disease, which may be due to the prenatal screening and diagnosis of RB procedure in developed regions and changes in newborn growth [45]. In addition, the present study found the inverse association between the SDI with mortality and burden of RB. Several factors may explain the higher ASMR and ASDR of RB in low SDI regions. Apart from potential shortcomings in social-economic background, low SDI regions might have less developed medical infrastructure and weaker public healthcare for children, exacerbating the disease burden [46–48].

Generally, a standardized classification system plays a critical importance of RB management, particularly given the disparities in treatment outcomes observed globally. The current landscape shows that RB lacks a universally adopted staging system, such as the AJCC TNM staging [49, 50], which complicates reliable comparisons of patient information and outcomes across institutions. The benefits of a uniform classification system are manifold; it would enhance the consistency of data collection and facilitate more effective cross-center analyses, ultimately leading to improved understanding of treatment gaps and patient care. By adopting a standardized framework, healthcare providers and researchers could better identify disparities in treatment access and quality, informing policymakers on how to allocate resources more effectively. We call upon stakeholders within the RB community to advocate for the adoption of such a classification system, emphasizing its potential to significantly improve patient outcomes through collaborative efforts.

The strengthen of current study lies in its provision of the most comprehensive global trends of the incidence and mortality of RB among children younger than 10 years,

including regional, sex-based, and SDI-based estimates. However, this study is limited to the general defects of GBD study. First, the GBD project estimates the impact of different health conditions by combining information about morbidity and premature mortality. However, the methodologies employed can be subject to biases and uncertainties, and the results may not align entirely with individual call detail records statistics or other sources of health information. Second, the accuracy of GBD estimates can be limited by the availability and quality of data, particularly in regions with poor health information systems. These estimates, therefore, might not fully capture the health condition or disease's scope or its variability across different populations. The process of synthesizing such sparse and unevenly distributed data is complex and can lead to substantial uncertainty in the findings. Another potential limitation includes difficulty in accounting for co-morbidity and the complexity of multiple health conditions in individuals. Another limitation of our study is the lack of tumor staging data in the GBD 2021 database. This absence restricts our ability to investigate the relationship between tumor staging and disease burden, particularly in understanding how variations in presentation stage impact treatment outcomes and mortality rates. Future research efforts should aim to integrate tumor staging information to provide a more nuanced understanding of prognosis in retinoblastoma and to guide targeted interventions. Finally, GBD database did not estimate data on the type of RB such as unilateral and bilateral disease. Even so, the GBD 2021 study has indeed made a considerable contribution to global health by providing comprehensive and comparable estimates of the burden of RB for global, regional, and national decision-making.

Conclusions

Although the incidence rate of childhood-onset RB has generally increased from 1990 to 2021, a significant decline was observed since 2019. Furthermore, there was a notable decrease in both the mortality and DALYs rates of RB during the study period. Of note, East Asia exhibited the most significant rise in the incidence rate of RB among children aged 0–9 years. While most regions experienced declining trends, Southern Sub-Saharan Africa was the only area to show a significant increase in both the mortality and DALYs rates of RB. In 2021, boys had slightly higher incidences and mortalities, but lower DALYs compared to girls. Early neonatal (0–6 days) and 2-4 year-old children were found to have the highest incidence, mortality and DALYs rates of RB. There was also marked heterogeneity between regions with different SDI levels. Countries with high SDI generally exhibited a greater incidence rate but lower mortality and DALYs rates among children of RB aged 0–9 years.

Abbreviations

AAPC	Average annual percentage change
ASDR	Age-standardised DALYs rate
ASIR	Age-standardised incidence rate
ASMR	Age-standardised mortality rate
CI	Confidence interval
DALYs	Disability-adjusted life years
EBRT	External beam radiation therapy
GBD	Global Burden of Disease
GHDx	Global Health Data Exchange
ICD	International Statistical Classification of Diseases
LMICs	Low- and middle-income countries
RB	Retinoblastoma
SDI	Sociodemographic index
SEER	Surveillance, Epidemiology, and End Results
UI	Uncertainty interval
WHO	World Health Organization
YLDs	Years lived with disability
YLLs	Years of life lost

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-024-03827-9.

Additional file1. Supplementary methods.

Additional file 2: Table S1. The data from Joinpoint regression analysis on the global incidence, deaths and DALYs of retinoblastoma in children aged younger than 10 years from 1990 to 2021. Table S2. Incidence, deaths and DALYs of retinoblastoma in children aged younger than 10 years in 1990 and 2021, and change from 1990 to 2021 by regions. Table S3. Incidence, deaths and DALYs of retinoblastoma in children aged younger than 10 years in 1990 and 2021, and change from 1990 to 2021 by countries. Fig S1. Global annual percent change of age-standardised rates of incidence, deaths, and DALYs of retinoblastoma in children aged younger than 10 years from 1990 to 2021. Fig S2. Age-standardised incidence rate of retinoblastoma in children aged younger than 10 years for 21 GBD regions (A) and 204 countries and territories (B) by sociodemographic index, 1990-2021. Fig S3. Age-standardised death rate of retinoblastoma in children aged younger than 10 years for 21 GBD regions (A) and 204 countries and territories (B) by sociodemographic index, 1990-2021. Fig S4. Age-standardised DALYs rate of retinoblastoma in children aged younger than 10 years for 21 GBD regions (A) and 204 countries and territories (B) by sociodemographic index, 1990-2021.

Acknowledgements

We thank the Institute for Health Metrics and Evaluation for sharing valuable GBD data.

Authors' contributions

All estimates presented in this article were provided by the GBD core team. CL, LYZ, LL, XHY, and XHY have verified the underlying data. CL, LL, JHJ, GYH, JZ, and MXZ provided data or critical feedback on data sources. CL and LL developed methods or computational machinery. CL, LJZ, JZ, YW, XH, CYC, and LL provided critical feedback on methods or results. All authors contributed to the drafting of the work or revised the article critically for important intellectual content. LL, HHY, and XHY contributed to managing the overall research enterprise. All authors read and approved the final manuscript.

Funding

This study was funded by GDPH Supporting Fund for Talent Program (KY0120220263), LiaoNing Revitalization Talents Program (XLYC2203192), National Natural Science Foundation of China (82271125, 81870663 and 82171075), Guangdong Basic and Applied Basic Research Foundation (2023B1515120028), the launch fund of Guangdong Provincial People's Hospital for NSFC (8217040449, 8227040339 and 8217040546), the Science and Technology Program of Guangzhou (20220610092), the Outstanding Young Talent Trainee Program of Guangdong Provincial People's Hospital (KJ012019087), the GDPH Scientific Research Funds for Leading

Medical Talents and Distinguished Young Scholars in Guangdong Province (KJ012019457), and Personalized Medical Incubator Project, The fund for Precison Medicine Research and Industry Development in SIMQ (2023–31).

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The protocol for this study was exempted by the Research Ethics Committee of the Guangdong Provincial People's Hospital (KY-Q-2022–495-01) because of the public availability of the data.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 8 July 2024 Accepted: 16 December 2024
Published online: 31 December 2024

References

1. Dimaras H, Corson TW, Cobrinik D, White A, Zhao J, Munier FL, et al. Retinoblastoma. Nat Rev Dis Prim. 2015;1:15021.
2. Fabian ID, Abdallah E, Abdullahi SU, Abdulqader RA, Adamou Boubacar S, Ademola-Popoola DS, et al. Global retinoblastoma presentation and analysis by national income level. JAMA Oncol. 2020;6(5):685–95.
3. Sherief ST, Wu F, O'Banion J, Teshome T, Dimaras H. Referral patterns for retinoblastoma patients in Ethiopia. BMC Health Serv Res. 2023;23(1):172.
4. Steliarova-Foucher E, Colombet M, Ries LAG, Moreno F, Dolya A, Bray F, et al. International incidence of childhood cancer, 2001–10: a population-based registry study. Lancet Oncol. 2017;18(6):719–31.
5. Usmanov RH, Kivelä T. Predicted trends in the incidence of retinoblastoma in the Asia-Pacific Region. Asia Pac J Ophthalmol (Phila). 2014;3(3):151–7.
6. Koochakzadeh L, Yekta A, Hashemi H, Pakzad R, Heydarian S, Khabazkhoob M. Epidemiological aspect of retinoblastoma in the world: a review of recent advance studies. Int J Ophthalmol. 2023;16(6):962–8.
7. El Hage S, Wakim E, Daou L, El Masri J, Salameh P. Epidemiology and Incidence of Retinoblastoma in the Middle East: a Nationwide Study in Lebanon. Cureus. 2021;13(10):e18696.
8. Abdelazeem B, Abbas KS, Shehata J, El-Shahat NA, Eltaras MM, Qaddoumi I, et al. Survival trends for patients with retinoblastoma between 2000 and 2018: What has changed? Cancer Med. 2023;12(5):6318–24.
9. GBD 2021 Forecasting Collaborators. Burden of disease scenarios for 204 countries and territories, 2022–2050: a forecasting analysis for the Global Burden of Disease Study 2021. Lancet. 2024;403(10440):2204–56.
10. GBD 2021 Risk Factors Collaborators. Global burden and strength of evidence for 88 risk factors in 204 countries and 811 subnational locations, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet. 2024;403(10440):2162–203.
11. GBD 2021 Diseases and Injuries Collaborators. Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet. 2024;403(10440):2133–61.
12. Skalet AH, Gombos DS, Gallie BL, Kim JW, Shields CL, Marr BP, et al. Screening children at risk for retinoblastoma: consensus report from the American association of ophthalmic oncologists and pathologists. Ophthalmology. 2018;125(3):453–8.
13. Vempuluru VS, Kaliki S. Screening for retinoblastoma: a systematic review of current strategies. Asia Pac J Ophthalmol (Phila). 2021;10(2):192–9.
14. Yun J, Li Y, Xu C-T, Pan B-R. Epidemiology and Rb1 gene of retinoblastoma. Int J Ophthalmol. 2011;4(1):103–9.
15. Lohmann D. Retinoblastoma. Adv Exp Med Biol. 2010;685:220–7.
16. Dimaras H, Dimba EAO, Gallie BL. Challenging the global retinoblastoma survival disparity through a collaborative research effort. Br J Ophthalmol. 2010;94(11):1415–6.
17. Canty CA. Retinoblastoma: an overview for advanced practice nurses. J Am Acad Nurse Pract. 2009;21(3):149–55.
18. Naseripour M. "Retinoblastoma survival disparity": the expanding horizon in developing countries. Saudi J Ophthalmol. 2012;26(2):157–61.
19. Chantada GL, Qaddoumi I, Canturk S, Khetan V, Ma Z, Kimani K, et al. Strategies to manage retinoblastoma in developing countries. Pediatr Blood Cancer. 2011;56(3):341–8.
20. Hadjistilianou D, Barchitta M, Defrancesco S. Covid-19 and retinoblastoma: How we manage it. Eur J Ophthalmol. 2020;30(5):NP6–10.
21. Fabian ID, Stacey AW, Bowman R, Khetan V, Blum S, Keren-Froim N, et al. Retinoblastoma management during the COVID-19 pandemic: a report by the Global Retinoblastoma Study Group including 194 centers from 94 countries. Pediatr Blood Cancer. 2021;68(1):e28584.
22. Zeng C, Cao W, Zhao T, Li L, Hou L. Hope level and associated factors among parents of retinoblastoma patients during COVID-19 pandemic: a cross-sectional study. BMC Psychiatry. 2021;21(1):391.
23. Bansal R, Aishwarya A, Rao R, Christy MC, Sen M, Regani H, et al. Impact of COVID-19 nationwide lockdown on retinoblastoma treatment and outcome: A study of 476 eyes of 326 children. Indian J Ophthalmol. 2021;69(10):2617–24.
24. Jiménez I, Laé M, Tanguy M-L, Savignoni A, Gauthier-Villars M, Desjardins L, et al. Craniofacial second primary tumors in patients with germline retinoblastoma previously treated with external beam radiotherapy: a retrospective institutional analysis. Pediatr Blood Cancer. 2020;67(4):e28158.
25. Liu JC, Givi B, Wolden S, Kleinerman RA, Dunkel IJ, Lee N, et al. Secondary skull base malignancies in survivors of retinoblastoma: the memorial sloan kettering cancer center experience. Skull Base. 2011;21(2):103–8.
26. Choi SY, Kim M-S, Yoo S, Cho C, Ji Y, Kim K, et al. Long term follow-up results of external beam radiotherapy as primary treatment for retinoblastoma. J Korean Med Sci. 2010;25(4):546–51.
27. Wen X, Fan J, Jin M, Jiang H, Li J, Han M, et al. Intravenous versus super-selected intra-arterial chemotherapy in children with advanced unilateral retinoblastoma: an open-label, multicentre, randomised trial. Lancet Child Adolesc Health. 2023;7(9):613–20.
28. Chernoff J. The two-hit theory hits 50. Mol Biol Cell. 2021;32(22):rt1.
29. Moll AC, Imhof SM, Bouter LM, Kuik DJ, Den Otter W, Bezemer PD, et al. Second primary tumors in patients with hereditary retinoblastoma: a register-based follow-up study, 1945–1994. Int J Cancer. 1996;67(4):515–9.
30. Sheehan AP. Retinoblastoma: early diagnosis is crucial. J Pediatr Health Care. 2020;34(6):601–5.
31. Zhang R, Dong L, Li R, Zhang K, Li Y, Zhao H, et al. Automatic retinoblastoma screening and surveillance using deep learning. Br J Cancer. 2023;129(3):466–74.
32. Wong ES, Choy RW, Zhang Y, Chu WK, Chen LJ, Pang CP, et al. Global retinoblastoma survival and globe preservation: a systematic review and meta-analysis of associations with socioeconomic and health-care factors. Lancet Glob Health. 2022;10(3):e380–9.

33. He MY, An Y, Gao YJ, Qian XW, Li G, Qian J. Screening of RB1 gene mutations in Chinese patients with retinoblastoma and preliminary exploration of genotype-phenotype correlations. Mol Vis. 2014;20:545–52.
34. Yang Y-Q, Li J, Yuan H-F. Epidemiology and risk factors of retinoblastoma in Chongqing area. Int J Ophthalmol. 2016;9(7):984–8.
35. Orjuela MA, Titievsky L, Liu X, Ramirez-Ortiz M, Ponce-Castaneda V, Lecona E, et al. Fruit and vegetable intake during pregnancy and risk for development of sporadic retinoblastoma. Cancer Epidemiol Biomarkers Prev. 2005;14(6):1433–40.
36. Leal-Leal C, Flores-Rojo M, Medina-Sansón A, Cerecedo-Díaz F, Sánchez-Félix S, González-Ramella O, et al. A multicentre report from the Mexican Retinoblastoma Group. Br J Ophthalmol. 2004;88(8):1074–7.
37. Kivelä T. The epidemiological challenge of the most frequent eye cancer: retinoblastoma, an issue of birth and death. Br J Ophthalmol. 2009;93(9):1129–31.
38. Canturk S, Qaddoumi I, Khetan V, Ma Z, Furmanchuk A, Antoneli CBG, et al. Survival of retinoblastoma in less-developed countries impact of socioeconomic and health-related indicators. Br J Ophthalmol. 2010;94(11):1432–6.
39. Fabian ID, Reddy A, Sagoo MS. Classification and staging of retinoblastoma. Community Eye Health. 2018;31(101):11–3.
40. Fabian ID, Khetan V, Stacey AW, Allen F, Ademola-Popoola DS, Berry JL, et al. Sex, gender, and retinoblastoma: analysis of 4351 patients from 153 countries. Eye (Lond). 2022;36(8):1571–7.
41. Li SY, Chen SCC, Tsai CF, Sheu SM, Yeh JJ, Tsai CB. Incidence and survival of retinoblastoma in Taiwan: a nationwide population-based study 1998–2011. Br J Ophthalmol. 2016;100(6):839–42.
42. Wong JR, Tucker MA, Kleinerman RA, Devesa SS. Retinoblastoma incidence patterns in the US surveillance, epidemiology, and end results program. JAMA Ophthalmol. 2014;132(4):478–83.
43. Holmes L, Pollack E, Berice BN, Halloran DR, Parson K, Badfford NT, et al. Survival disadvantage of male children with retinoblastoma in the United States: Surveillance Epidemiology and End Results (2000–2017) Evidence. Cancer Med. 2023;12(4):4626–37.
44. Chen J, Cao X, Xu S, Chen X, Xie R, Ye G, et al. Global, regional, and national burden of retinoblastoma in infants and young children: findings from the global burden of disease study 1990–2021. EClinicalMedicine. 2024;76:102860.
45. Rodriguez A, Kelley C, Patel A, Ramasubramanian A. Prenatal diagnosis of retinoblastomas: a scoping review. Int J Gen Med. 2023;16:1101–10.
46. Miranda J, Miller S, Alfieri N, Lalonde A, Ivan-Ortiz E, Hanson C, et al. Global health systems strengthening: FIGO's strategic view on reducing maternal and newborn mortality worldwide. Int J Gynaecol Obstet. 2024;165(3):849–59.
47. Fentie EA, Asmamaw DB, Negash WD, Belachew TB, Amare Baykeda T, Addis B, et al. Spatial distribution and determinants of barriers of health care access among female youths in Ethiopia, a mixed effect and spatial analysis. Sci Rep. 2023;13(1):21517.
48. Bradford DRR, Swift A, Allik M, McMahon AD, Brown D. Physical health of care-experienced young children in high-income countries: a scoping review. Lancet. 2023;402(Suppl 1):S28.
49. Tomar AS, Finger PT, Gallie B, Mallipatna A, Kivelä TT, Zhang C, et al. A multicenter, international collaborative study for American joint committee on cancer staging of retinoblastoma: part ii: treatment success and globe salvage. Ophthalmology. 2020;127(12):1733–46.
50. Tomar AS, Finger PT, Gallie B, Mallipatna A, Kivelä TT, Zhang C, et al. A multicenter, international collaborative study for American joint committee on cancer staging of retinoblastoma: part i: metastasis-associated mortality. Ophthalmology. 2020;127(12):1719–32.

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