Global, regional, and national burden of retinoblastoma in infants and young children: findings from the global burden of disease study 1990–2021

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Summary

Background Retinoblastoma is considered a lethal but curable malignancy often presenting in childhood. We investigated its global, regional, and national burden among infants and young children from 1990 to 2021.

Methods We obtained data on retinoblastoma incidence, prevalence, mortality, and disability-adjusted life years (DALYs) from the Global Burden of Diseases, Injuries, and Risk Factors Study 2021. Trends were analysed using joinpoint regression to calculate annual percentage changes. Spearman's rank correlation and locally estimated scatterplot smoothing regression were used to assess the relationship between retinoblastoma burden and sociodemographic index.

Findings In 2021, the global incidence, prevalence, mortality, and DALYs of retinoblastoma were 0.82 (95% uncertainty interval [UI], 0.48–1.10), 7.46 (95% UI, 4.42–10.08), 0.37 (95% UI, 0.22–0.51), and 32.81 (95% UI, 19.9–45.21), respectively. From 1990 to 2021, the global incidence and prevalence rates of retinoblastoma increased, with average annual percentage changes (AAPCs) of 0.67 (95% confidence interval [CI], 0.49–0.85] and 0.68 (95% CI, 0.50–0.86), respectively. Conversely, those of related mortality and DALYs decreased, with AAPCs of −0.64 (95% CI, −0.79 to −0.49) and −0.63 (95% CI, −0.78 to −0.48), respectively. Children aged 2–4 years and those in low-income regions exhibited the highest burden. Negative correlations were found between sociodemographic index and retinoblastoma burden.

Interpretation Advancements in retinoblastoma detection and treatment have increased its reported incidence and prevalence while reducing its mortality and DALYs. Nonetheless, substantial socioeconomic and geographic disparities persist. In low-income countries, the incidence has decreased, possibly reflecting challenges such as limited healthcare access and underreporting, necessitating targeted interventions and improved healthcare access.

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Keywords: Retinoblastoma; Burden; Infants; Children

Introduction

Retinoblastoma can manifest in one or both eyes and is considered one of the most prevalent intraocular cancer in childhood. Epidemiological studies conducted in numerous countries and regions, such as the United States and the United Kingdom,[1,2] have estimated its incidence at 40–60 cases per million live births, which translates to approximately 1 in every 16,000 to 24,000 live births. According to the Global Retinoblastoma Outcome Study by the Global RB Study Group, retinoblastoma mortality is rare in high-income nations, but in low-income countries, the projected 3-year survival rate is just over 50%.[3] Approximately 25% of children diagnosed with retinoblastoma in African participating

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Research in context

Evidence before this study

Retinoblastoma is a lethal but curable malignancy that presents primarily in childhood. Epidemiological studies conducted in numerous countries and regions estimated its incidence at 40–60 cases per million live births, which translates to approximately 1 in every 16,000 to 24,000 live births. Whereas prior studies have provided crucial insights into the global burden of retinoblastoma, including its prevalence and outcomes, further research is needed to explore the temporal trends and regional variations among infants and young children, providing valuable insights for targeted interventions.

Added value of this study

In this study, we used the Global Burden of Disease Study (GBD) 2021 to assess the global, regional, and national burden of retinoblastoma, including incidence, prevalence, mortality, and disability-adjusted life years (DALYs), in 204 countries and territories, stratified by age, sex, income, region, country and territory. From 1990 to 2021, the incidence and prevalence rates of retinoblastoma among infants and young children increased globally, whereas the rates of related mortality and DALYs decreased. Significant disparities were observed by income and region, with the highest burden in low-income regions and negative correlations were found between sociodemographic indices and retinoblastoma burden.

Implications of all the available evidence

Advancements in retinoblastoma detection and treatment have led to increased incidence and prevalence but reduced mortality and DALYs globally, with notable variations between different income regions. In middle-income regions, the observed increase in burden may be largely attributed to enhanced diagnostic capabilities and better healthcare access; however, in low-income countries, the incidence has decreased, possibly reflecting challenges such as limited healthcare access and underreporting. This underscores the need for targeted interventions and improved healthcare access, particularly in lower-income regions, to ensure that the benefits of early detection and advanced treatment are equitably benefited.

centres die from the disease within 1 year.[4] The mortality rates due to retinoblastoma were 8.8% and 8% among Americans and Asians, respectively.[5,6]

Retinoblastoma poses a serious threat to life if not treated promptly. Advanced tumours can invade the orbit, extend through the optic nerve to the central nervous system, or metastasise to the bone marrow and internal organs. Thus, early detection and prompt treatment are crucial to improve morbidity and mortality.[7] Accordingly, the primary objective of retinoblastoma treatment is to save the child's life by detecting the tumour early and preventing its spread, while preserving the eye and improving visual function are secondary objectives.

While tumours are still small, early detection and intervention can result in nearly 100% survival rates.[8] Notably, survival rates vary across countries and ethnic groups. In some developed nations, the overall 5-year survival rate ranges from 83% to 97%, whereas it is significantly lower, between 20% and 48%, in developing countries, which represent the highest burden of retinoblastoma globally.[9,10] The better prognosis for patients with retinoblastoma in developed regions can be attributed to multiple factors, such as established specialised referral centres and enhanced understanding of related genetic factors[11]; as such, retinoblastoma is considered curable.[12] Conversely, in developing nations, the prognosis remains poor, likely owing to factors such as limited access to specialised medical care and pathology services,[7,13,14] leading to delayed diagnosis and treatment.[15]

Existing research has provided important insights into the local burden of the disease; however, these studies are often limited by data constraints and methodological differences. The actual global burden of retinoblastoma remains unclear, as are the variations in burden across different regions over time. To address these gaps, we aimed to detail the burden of retinoblastoma, including its incidence, prevalence, mortality, disability-adjusted life years (DALYs), and related trends, among infants and young children from 1990 to 2021 using the Global Burden of Disease Study (GBD) dataset.[16–18] This information is crucial for developing effective global prevention and control strategies.

Methods

Study design

This was a population-based retrospective analysis of repeated cross-sectional data from the GBD 2021 obtained from the Global Health Data Exchange database.[18] This comprehensive dataset covers the global burden of 371 diseases and injuries, including retinoblastoma, across 21 GBD regions and 204 countries and territories from 1990 to 2021. The methodology employed in the GBD 2021 has been extensively documented in prior studies.[16,17] A brief description is provided in Supplementary Appendix 1.[16,17]

Ethics

This study complied with the principles outlined in the Declaration of Helsinki and strictly adheres to the Guidelines for Accurate and Transparent Health Estimates Reporting statement. The Medical Ethics Committee of the Zhongshan Ophthalmic Center at Sun Yat-sen

University, Guangzhou, China, approved this study and waived the requirement for obtaining informed consent (approval number: 2023KYPJ095-2). Access to and use of these datasets are granted in accordance with the Non-Commercial User Agreement provided by the Institute for Health Metrics and Evaluation.[19]

Case definition and data collection

Retinoblastoma is classified as a GBD cause of cancer corresponding to ICD-10 codes C69.2–C69.22. The GBD addressed missing raw epidemiological data by estimating the burden through a hierarchical approach, cascading down five levels of geographical hierarchy. Data from higher-level locations in the hierarchy served as priors to estimate epidemiological parameters for lower-level locations. Additionally, location-specific covariates were incorporated to inform the burden estimates in regions where data were lacking.[16,17] The input data and methodological summary for retinoblastoma are detailed in Supplementary Appendix 2.[16,17]

For the present study, we collected data on infants and young children under the age of 5 years, as this is the age group most commonly affected by retinoblastoma.[20] Retinoblastoma indicators were collected for both sexes across 5 age groups (<28 days, 1–5 months, 6–11 months, 12–23 months, and 2–4 years), 21 region groups with geographical and epidemiological similarity, and 4 income groups based on the World Bank criteria. Additionally, the GBD 2021 calculated the sociodemographic index (SDI) for each country, a parameter reflecting the social and economic conditions influencing health outcomes. From 0 to 1, the SDI is determined by the geometric mean of three components: the total fertility rate in individuals aged under 25, average years of education for individuals aged 15 and above, and lag-distributed income per capita. An SDI of 0 indicates the minimal level of education, lowest income per capita, and highest fertility rate.[21]

Statistics

We analysed the global burden of retinoblastoma by assessing the associated incidence, prevalence, DALYs, and mortality; these data and their corresponding rates were obtained directly from the GBD 2021 dataset.[18] All rates are reported per 100,000 population. The 95% uncertainty intervals (UIs) were derived by the GBD study using the 2.5th and 97.5th percentiles from a set of 1000 ordered estimates. To achieve this, the GBD study generated 1000 draws from the posterior distribution and employed a bootstrapping method using sampling with replacement at each step of the estimation process, enabling the quantification and propagation of uncertainty across all epidemiological variables within the GBD framework.[16,17] Using 1000 bootstrap replications was sufficiently large in most circumstances, providing a practical compromise between accuracy and efficiency. Increasing the bootstrap replications does not enhance the information content of the original data; it can only mitigate the impact of random sampling mistakes that may result from a bootstrap analysis. Increasing the number of bootstrap replications beyond 1000 results in limited enhancements in the estimate of UI, but it requires a much higher amount of computation, which is unnecessary.[22]

To evaluate the burden trends, we employed joinpoint regression analysis. This method assumes a linear trend in disease burden over the study period. An inflection point, or joinpoint, is introduced to represent a change in this trend. A permutation test is applied to compare the joinpoint model to the null model to assess statistical significance, and the joinpoint is retained if found to be statistically significant. This process was repeated with Bonferroni correction applied to account for multiple comparisons, ultimately identifying the optimal joinpoints from a total of 4499 Monte Carlo permutations, which represents the default sample size for the permuted datasets.[23] To avoid overfitting, we set the maximum number of allowed joinpoints to five, which helps control the complexity of the model, ensuring that it captures the main trends in the data rather than overfitting the noise.[23]

We characterised non-linear and linear trends using this method by analysing their inflection points and corresponding weights. The degree of change was quantified using annual percentage change (APC) and average APC (AAPC) values, and their corresponding 95% confidence intervals (CIs). The APC is a statistical measure of the rate of change between different inflection points, representing the slope for each designated time interval. The AAPC is an analytical measure providing an overall summary of the trend over a specified period, showing whether the trend increased, decreased, or remained stable.[24] Determining the AAPC involved computing a weighted average of the APC values derived from the joinpoint model. Each APC value was weighted according to the length of its respective time period. AAPCs were calculated for the timeframe from 1990 to 2021. If the interval does not include a zero, the AAPC is considered statistically significant. We also examined the relationship between the burden of retinoblastoma and the SDI using Spearman's rank correlation, given that neither variable followed a normal distribution (all $P < 0.0001$) according to the Shapiro–Wilk test, and applied locally estimated scatterplot smoothing.

The estimated parameters were obtained using Joinpoint Trend Analysis Software (version 5.0.2; National Cancer Institute, Bethesda, MD, USA), developed by the National Cancer Institute. Calculations and graph drawings were performed using R (version 4.2.2, Posit PBC, Boston, MA, USA).

Role of funding source

The funding organisations had no role in the study design, data collection, data analyses, interpretation, or writing of the report.

Results

Global retinoblastoma burden and trends

The trends in retinoblastoma incidence, prevalence, mortality, and DALYs (per 100,000 population) among infants and children under the age of 5 years between 1990 and 2021 are presented in Tables 1 and 2, and Supplementary Tables S1 and S2

Globally, the incidence and prevalence rates were increased from 1990 to 2019, followed by a dramatic decrease from 2019 to 2021, with an overall increasing trend during the study period, as reflected by AAPCs of 0.67 (95% CI, 0.49–0.85) and 0.68 (95% CI, 0.50–0.86), respectively. Conversely, the mortality and DALY rates were decreased from 1990 to 2021, with AAPCs of –0.64 (95% CI, –0.79 to –0.49) and –0.63 (95% CI, –0.78 to –0.48), respectively. An exception from this decreasing trend was observed from 2002 to 2014, with APCs of 0.17 and 0.20, respectively (Fig. 1).

Regarding sex, no substantial differences were observed in the burden and trends of retinoblastoma between males and females. In terms of age, the incidence, prevalence, mortality, and DALYs (per 100,000 population) increased with age, with children aged 2–4 years exhibiting the highest incidence [0.91 (95% UI, 0.54–1.27)], prevalence [8.26 (95% UI, 4.92–11.56)], mortality [0.44 (95% UI, 0.26–0.62)], and DALYs [38.79 (95% UI, 23.3–54.43)] in 2021. From 1990 to 2021, children aged 12–23 months showed the most significant increases in incidence and prevalence, with AAPCs of 1.37 (95% CI, 1.06–1.67) and 1.38 (95% CI, 1.07–1.68), respectively. The overall trends for mortality and DALYs were relatively consistent across different age groups, although the degree of change varied.

Among income groups, the low-income group had the highest incidence [0.93 (95% UI, 0.53–1.42)], prevalence [8.43 (95% UI, 4.84–12.9)], mortality [0.79 (95% UI, 0.47–1.16)], and DALYs [69.02 (95% UI, 41.59–102.15)]. However, unfavourable increasing trends in incidence and prevalence were also observed in the upper-middle-income group [AAPC: 1.94 (95% CI, 1.62–2.27) and 1.95 (95% CI, 1.62–2.28), respectively] and lower-middle-income group [AAPC: 0.87 (95% CI, 0.72–1.02) and 0.88 (95% CI, 0.73–1.03), respectively]. The overall trends for mortality and DALYs were relatively consistent across different income groups, although the degree of change varied.

Retinoblastoma burden and trends by region

The burden and trends of retinoblastoma varied significantly across regions. In terms of incidence and prevalence, Eastern Sub-Saharan Africa showed the highest rates in 2021, with an incidence of 1.83 (95% UI, 1.11–2.9) and a prevalence of 16.68 (95% UI, 10.1–26.44). In contrast, the Caribbean had the lowest incidence and prevalence, at 0.09 (95% UI, 0.05–0.16) and 0.84 (95% UI, 0.44–1.49), respectively. From 1990

	Cases, 1990	Prevalence, 1990	Cases, 2021	Prevalence, 2021	AAPC, 1990–2021
Worldwide	36,588.8 (23,452.59–47,353.88)	5.9 (3.78–7.64)	49,087.8 (29,069.66–66,314.27)	7.46 (4.42–10.08)	0.68 (0.5–0.86)
Sex					
Male	18,636.66 (10,822.22–25,594.52)	5.83 (3.39–8.01)	25,203.91 (13,951.78–35,321.22)	7.41 (4.1–10.39)	0.71 (0.56–0.86)
Female	17,952.14 (9760.18–24,534.99)	5.98 (3.25–8.17)	23,883.89 (11,352.69–34,262.99)	7.51 (3.57–10.77)	0.71 (0.5–0.92)
Age					
<28 days	289.65 (194.45–371.29)	2.89 (1.94–3.7)	338.79 (220.46–459.19)	3.48 (2.26–4.71)	0.62 (0.42–0.83)
1–5 months	2100.96 (1224.67–2841.44)	3.85 (2.24–5.2)	2710.88 (1628.04–3741.96)	5.04 (3.03–6.96)	0.9 (0.69–1.11)
6–11 months	2531.4 (1358.53–3533.88)	4.01 (2.15–5.6)	3365.16 (1840.33–4891.94)	5.33 (2.91–7.74)	0.98 (0.65–1.32)
12–23 months	5875.37 (4002.51–7589.99)	4.71 (3.21–6.09)	9367.83 (5185.15–13,077.7)	7.3 (4.04–10.18)	1.38 (1.07–1.68)
2–4 years	25,791.41 (16,315.5–33,747.24)	7.02 (4.44–9.18)	33,305.13 (19,825.13–46,592.41)	8.26 (4.92–11.56)	0.43 (0.27–0.59)
Income					
High income	6422.46 (5332.98–7683.09)	9.02 (7.49–10.79)	4921.96 (3705.11–6186.84)	8.03 (6.04–10.09)	–0.37 (–1.47 to 0.74)
Upper-middle income	8466.92 (5440.44–12,772.64)	4.16 (2.67–6.28)	12,736.59 (6517.67–19,152.49)	8.07 (4.13–12.13)	1.95 (1.62–2.28)
Lower-middle income	14,905.35 (7707.48–21,327.27)	5.18 (2.68–7.41)	22,548.66 (12,191.17–33,342.61)	6.76 (3.66–10)	0.88 (0.73–1.03)
Low income	6775.72 (3917.37–9588.41)	11.87 (6.86–16.8)	8859.66 (5086.81–13,555.86)	8.43 (4.84–12.9)	–1.09 (–1.31 to –0.88)

AAPC, average annual percentage change.

Table 1: **Prevalence of retinoblastoma among infants and young children and related AAPCs from 1990 to 2021 at global level.**

	Cases, 1990	Mortality, 1990	Cases, 2021	Mortality, 2021	AAPC, 1990–2021
Worldwide	2802.78 (1576.49–3699.56)	0.45 (0.25–0.6)	2439.3 (1477.05–3361.68)	0.37 (0.22–0.51)	−0.64 (−0.79 to −0.49)
Sex					
Male	1429.4 (700.82–1982.37)	0.45 (0.22–0.62)	1248.61 (654.41–1838.37)	0.37 (0.19–0.54)	−0.62 (−0.68 to −0.56)
Female	1373.38 (577.16–1913.7)	0.46 (0.19–0.64)	1190.69 (552.52–1691.4)	0.37 (0.17–0.53)	−0.65 (−0.8 to −0.5)
Age group					
<28 days	20.9 (12.12–27.31)	0.21 (0.12–0.27)	13.9 (7.94–19.24)	0.14 (0.08–0.2)	−1.22 (−1.32 to −1.11)
1–5 months	170.01 (86.15–242.59)	0.31 (0.16–0.44)	131.12 (74.33–183.28)	0.24 (0.14–0.34)	−0.83 (−1.02 to −0.65)
6–11 months	218.91 (102.9–319.8)	0.35 (0.16–0.51)	206.75 (110.5–320.65)	0.33 (0.17–0.51)	−0.19 (−0.33 to −0.04)
12–23 months	365.18 (207.56–488.87)	0.29 (0.17–0.39)	306.37 (175.64–426.52)	0.24 (0.14–0.33)	−0.66 (−0.76 to −0.56)
2–4 years	2027.79 (1150.11–2694.44)	0.55 (0.31–0.73)	1781.16 (1068.08–2501.36)	0.44 (0.26–0.62)	−0.72 (−0.92 to −0.52)
Income group					
High income	36.28 (29.8–45.16)	0.05 (0.04–0.07)	10.14 (8.49–12.31)	0.02 (0.01–0.02)	−3.76 (−4.37 to −3.14)
Upper-middle income	509.87 (337.81–687.01)	0.24 (0.16–0.32)	143.26 (88.64–192.14)	0.09 (0.05–0.12)	−3.46 (−3.7 to −3.21)
Lower-middle income	1511.12 (775.8–2122.25)	0.54 (0.28–0.76)	1414.24 (824.06–1972.73)	0.44 (0.26–0.61)	−0.64 (−0.79 to −0.5)
Low income	744.31 (429.92–1057.06)	1.22 (0.7–1.73)	870.48 (525.04–1288.44)	0.79 (0.47–1.16)	−1.37 (−1.58 to −1.17)

AAPC, average annual percentage change.

Table 2: **Mortality of retinoblastoma among infants and young children and related AAPCs from 1990 to 2021 at global level.**

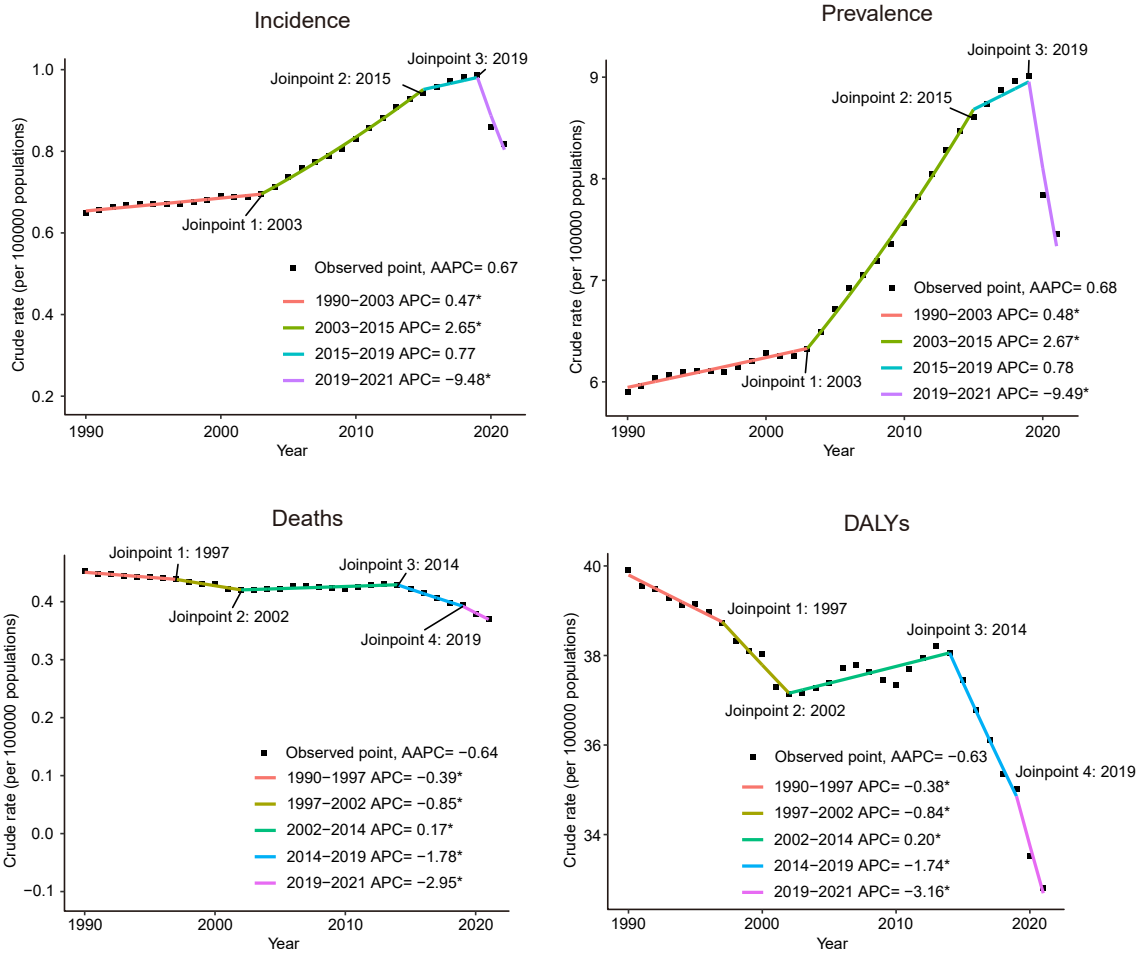

Fig. 1: Joinpoint regression analysis of the global incidence, prevalence, mortality, and DALYs of retinoblastoma among infants and children under the age of 5 years from 1990 to 2021. APC, annual percentage change; AAPC, average annual percentage change; DALYs, disability-adjusted life years.

to 2021, East Asia exhibited the highest increases in incidence and prevalence, with AAPCs of 2.86 (95% CI, 2.28–3.44) and 2.87 (95% CI, 2.29–3.45), respectively. Conversely, Australasia showed the most substantial decreases, with AAPCs of –3.83 (95% CI, –7.12 to –0.42) for incidence and –3.82 (95% CI, –7.12 to –0.41) for prevalence (Supplementary Tables S3 and S4).

Regarding mortality and DALYs, Eastern Sub-Saharan Africa had the highest rates in 2021, with mortality at 1.52 (95% UI, 0.99–2.32) and DALYs at 133.48 (95% UI, 86.83–204.07). In contrast, Australasia had the lowest rates in both categories. From 1990 to 2021, Southern Sub-Saharan Africa exhibited the highest increases in mortality and DALYs, with AAPCs of 1.1 (95% CI, 0.49–1.72) for mortality and 1.11 (95% CI, 0.5–1.72) for DALYs. Conversely, Australasia showed the most substantial decreases, with AAPCs of –6.83 (95% CI, –9.31 to –4.29) for mortality and –5.8 (95% CI, –8.22 to –3.32) for DALYs (Supplementary Tables S5 and S6).

Retinoblastoma burden and trends by country/territory

In 2021, Tokelau had the highest incidence [12.58 (95% UI, 2.67–40.73)], prevalence [115.35 (95% UI, 24.45–373.31)], mortality [3.93 (95% UI, 0.8–12.97)], and DALYs [347.74 (95% UI, 70.84–1147.99)]. In contrast, Seychelles consistently had the lowest values in these categories.

From 1990 to 2021, Tokelau exhibited the highest increases in incidence [AAPC: 19.43 (95% CI, 15.33–23.67)], prevalence [AAPC: 19.43 (95% CI, 15.33–23.68)], mortality [AAPC: 15.59 (95% CI, 11.36–19.99)], and DALYs [AAPC: 15.64 (95% CI, 11.41–20.02)]. Conversely, Kuwait showed the most substantial decreases in incidence [AAPC: –8.46 (95% CI, –10.75 to –6.11)] and prevalence [AAPC: –8.46 (95% CI, –10.74 to –6.12)], while Cuba had the greatest reductions in mortality [AAPC: –11.59 (95% CI, –16.48 to –6.42)] and DALYs [AAPC: –11.49 (95% CI, –16.38 to –6.32)] (Fig. 2 and Supplementary Figure S1, Supplementary Tables S7–S10).

Retinoblastoma burden by SDI

At the regional level, we observed V-shaped associations between the SDI and retinoblastoma incidence and prevalence from 1990 to 2021, with significant positive correlations between the SDI and both incidence (Spearman's $\rho = 0.11$, $P = 0.00019$) and prevalence rates (Spearman's $\rho = 0.12$, $P = 0.00011$). Conversely, the associations between the SDI and mortality and DALYs were L-shaped, with significant negative correlations between the SDI and both mortality (Spearman's $\rho = -0.84$, $P < 0.0001$) and DALYs (Spearman's $\rho = -0.83$, $P < 0.0001$) (Fig. 3).

At the national level, negative correlations were observed between the SDI and both mortality (Spearman's $\rho = -0.73$, $P < 0.0001$) and DALYs (Spearman's $\rho = -0.72$, $P < 0.0001$). Significant negative associations

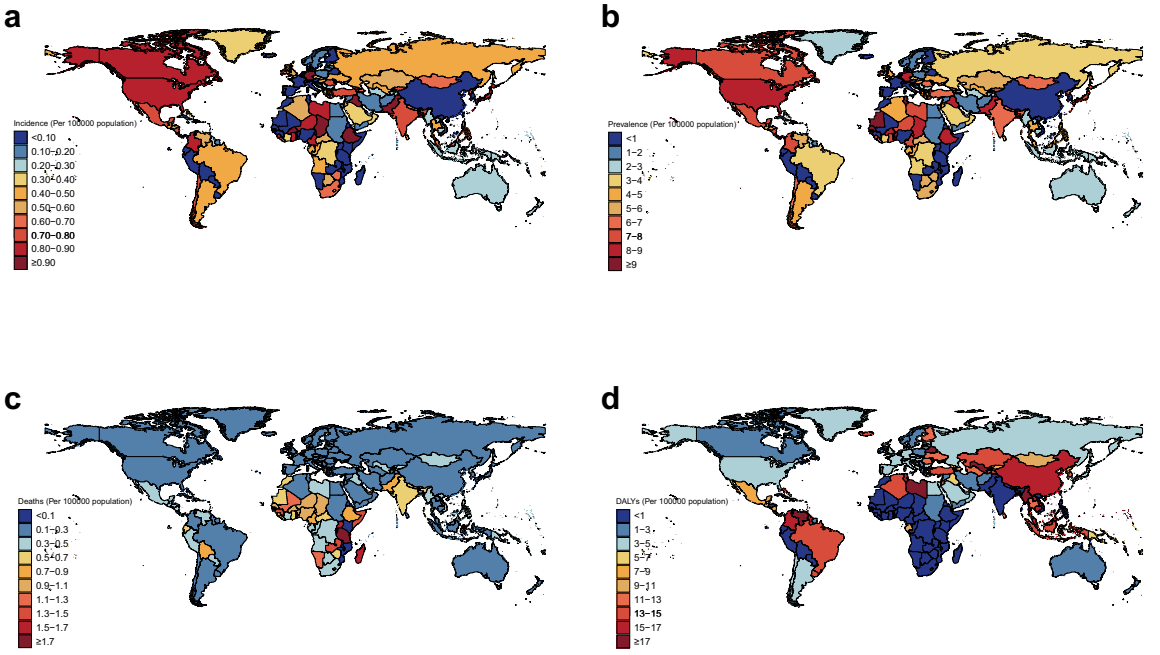

Fig. 2: Global incidence (a), prevalence (b), mortality (c), and DALYs (d) of retinoblastoma among infants and children under the age of 5 years in 2021. DALYs, disability-adjusted life years.

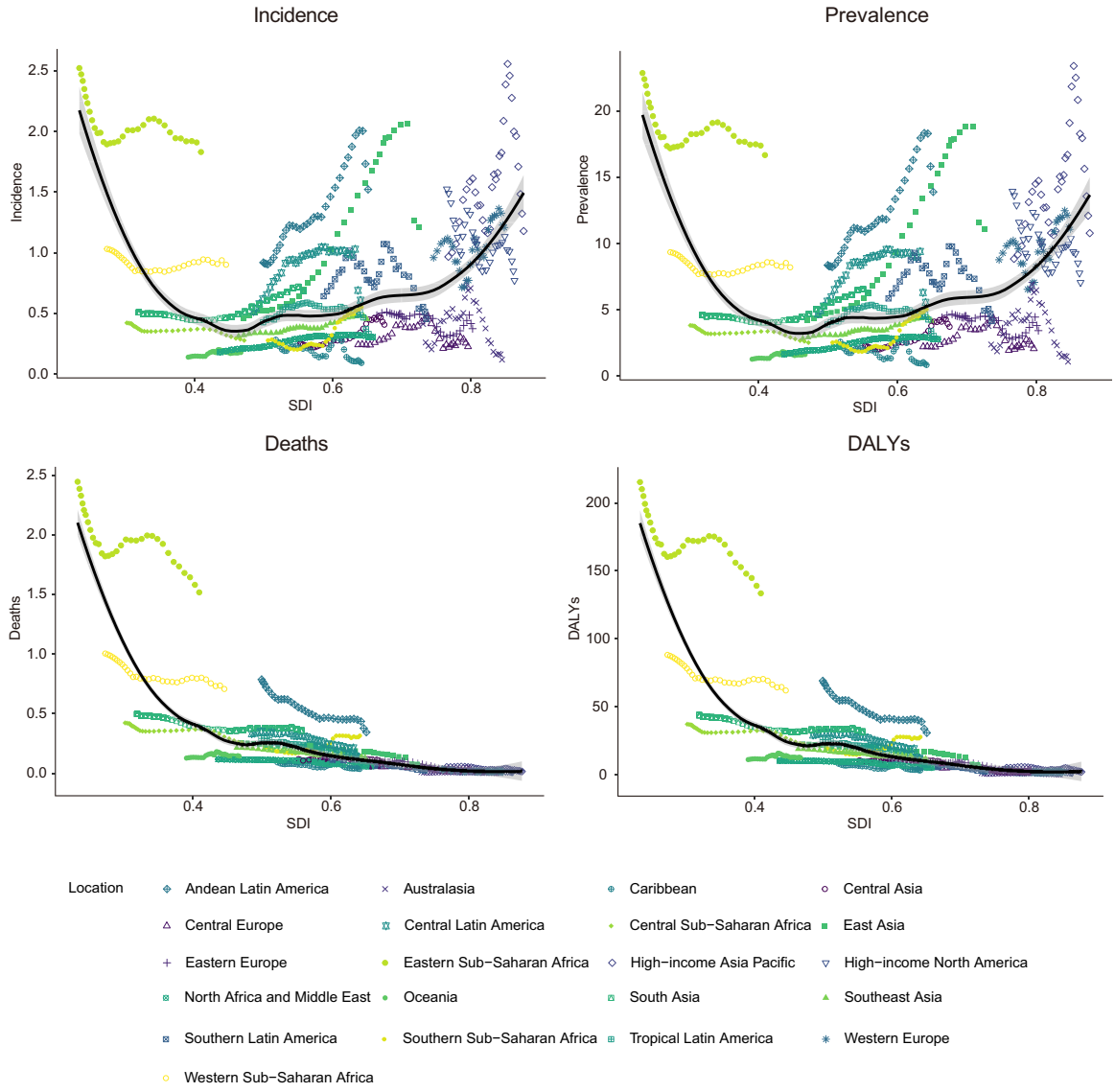

Fig. 3: Incidence, prevalence, mortality, and DALYs of retinoblastoma among infants and children under the age of 5 years from 1990 to 2021 in 21 regions according to the SDI. DALYs, disability-adjusted life years; SDI, sociodemographic index.

were also found with incidence (Spearman's ρ = –0.16, P = 0.025) and prevalence (Spearman's ρ = –0.16, P = 0.026) (Supplementary Figures S2 and S3).

Discussion

This study describes the global burden of retinoblastoma and trends among infants and young children under 5 years of age between 1990 and 2021. During the study period, the global incidence and prevalence of retinoblastoma in this population significantly increased, while mortality and DALYs decreased. Children aged 2–4 years exhibited the highest burden. Significant income-related disparities were observed, with low-income groups bearing the highest overall burden, while middle-income groups showed increasing trends in incidence and prevalence. Negative correlations were found between the SDI and retinoblastoma burden, highlighting the influence of socioeconomic factors on the burden of retinoblastoma.

The rise in the incidence and prevalence of retinoblastoma from 1990 to 2021 in middle-income countries, including upper- and lower-middle income countries, can be explained by multiple factors. Enhanced diagnostic methods and improved reporting systems, driven by greater public awareness and better healthcare access, have likely contributed.[6] Additionally, there may be a genuine increase in cases owing to

improved survival rates, reproductive capabilities, and confidence among survivors of heritable retinoblastoma.[25] Despite the rising incidence and prevalence, the significant decrease in mortality and DALYs indicates substantial progress in treatment and management practices. Advancements in genetic diagnosis and treatment have led to decreased visual impairment, enhanced eye preservation, and higher survival rates.[26] These improvements have, in turn, reduced the selection coefficient and increased overall fitness.[15] The increasing prevalence of germline *RB1* pathogenic variant carriers in Europe illustrates the relaxation of natural selection pressure caused by medical treatments for a previously fatal disorder within only a few generations.[25]

The burden and adverse outcomes of retinoblastoma were highest among children aged 2–4 years, primarily due to delayed detection and the nature of the disease. Older patients and those with heritable traits face higher risks for systemic metastasis and mortality. These children often have poorer outcomes due to germline mutations, greater tumour load, higher risk for secondary cancers, and the difficult decision of caregivers' when considering bilateral enucleation, and the subsequent effect this may pose to the patients' quality of life. Additionally, older children might experience a higher risk of local treatment challenges.[10]

Development-related disparities were pronounced, with lower-level income and SDI groups experiencing the highest burden of retinoblastoma. This disparity is largely due to unequal access to healthcare, diagnostic facilities, and treatment options.[15] Delayed diagnosis and treatment abandonment contribute significantly to poor outcomes in affected children.[27] In some regions, religious beliefs and social stigma lead families to reject enucleation, even for unilateral cases, resulting in delayed cure and increased metastatic disease.[28] Overcoming these challenges necessitates that health ministries should establish clinical guidelines across all levels of care, backed by specialised retinoblastoma teams and eye cancer experts, ensuring skill transfer to lower-income countries.[29,30] Early diagnosis and timely enucleation are essential. Yet, the absence of advanced treatments, such as external beam radiotherapy and salvage techniques, in lower-income nations worsens these inequities.[15]

Regionally, Sub-Saharan Africa exhibited the highest burden and greatest increase in adverse outcomes of retinoblastoma, highlighting the challenges associated with paediatric cancers in low-resource settings. In contrast, the rise in incidence and prevalence in East Asia is likely due to improved diagnostics and epidemiological surveillance. Australasia demonstrated significant declines in mortality and DALYs, probably attributed to robust screening, healthcare systems, and advanced treatments. Genetic testing for the *RB1* gene, which has been available for nearly three decades, remains limited in most regions, with only 36% availability even in Asia.[6,31] Australia illustrates the cost-effectiveness of conducting genetic diagnoses for retinoblastoma.[32] These regional disparities further underscore the need for localised healthcare strategies tailored to specific regional needs and capacities.

To tackle these global challenges, the World Health Organization's Global Initiative for Childhood Cancer seeks to increase the survival rate of major childhood cancers, including retinoblastoma, to 60% by 2030 through coordinated international efforts.[33] This requires enhancing public awareness, early diagnosis, and treatment access through national and international collaboration. Improving public awareness and reforming healthcare systems to provide easy access to services and universal health insurance is essential for ensuring all children can receive timely, cost-free diagnosis and treatment at tertiary health centres.[34]

The availability of resources significantly affects treatment outcomes within a country. Common primary treatments include intravenous chemotherapy and enucleation. However, crucial treatments for advanced cases, such as intravitreal chemotherapy, intra-arterial chemotherapy, external beam radiotherapy, and plaque radiotherapy, are often less available, reducing the potential to save affected eyes, particularly in persistent or recurrent tumours.[6] Enhancing the availability of these advanced treatments is vital for improving outcomes and preserving vision in affected children. It is essential that health ministries play an active role in the development and dissemination of clinical guidelines for retinoblastoma care. Current guidelines, such as those available in Canada, provide valuable frameworks tailored to the specific resources and needs of these regions.[35,36] Expanding such region-specific guidelines is a crucial step in ensuring that best practices are adopted and that efforts to reduce mortality and improve DALYs are effectively implemented.

Early detection of retinoblastoma is crucial for achieving optimal visual and survival outcomes. The American Association of Ophthalmic Oncologists and Pathologists has emphasised the importance of genetic counselling and testing for risk stratification.[37] They propose a risk-based approach for ophthalmic screenings. Genetic testing is crucial in this framework: a positive result for *RB1* mutation signifies a high risk of developing the disease. In contrast, a negative result implies a risk comparable to that of the general population, negating the need for specialised screening.[37] Additionally, adult survivors of hereditary retinoblastoma face an increased risk for secondary cancers. Prompt evaluation of symptoms and regular dermatologic assessments have been recommended for long-term follow-up.[38]

The current study has some limitations. First, the GBD estimates the disease burden for all regions using available epidemiological data, which are often lacking or of poor quality in some regions, leading to shortfalls in reporting and potentially affecting our results.[16,17]

There is an urgent need for improved data collection and reporting mechanisms in low-income regions to enhance the accuracy and reliability of future research. Additionally, the observed decrease in incidence and prevalence rates from 2019 to 2021 may be attributed to the global COVID-19 pandemic. The widespread lockdowns and restrictions during this period may have affected healthcare access and the reporting of new cases, potentially obscuring the observed trend. Second, GBD analyses aim to account for uncertainty across various data types and processes. In this secondary analysis, we used the joinpoint method to estimate the UIs under the assumption of non-constant variance. Despite these efforts, capturing all sources of uncertainty throughout the entire burden estimation pipeline remains a significant challenge.[16,17] This study focused on infants and young children for mortality and DALYs analysis, as retinoblastoma primarily affects this age group. However, the lifelong impact of retinoblastoma still needs to be highlighted. Further research is needed to explore these long-term outcomes in the population context. In addition, per the GBD methodology, survivors living beyond 10 years are considered cured. While this approach may not fully capture the lifelong impact of retinoblastoma, particularly for those facing long-term health challenges, the limitation is somewhat mitigated by our focus on a younger population. Nonetheless, this remains an area to be addressed more comprehensively in future research.

From 1990 to 2021, significant global efforts have improved retinoblastoma's early detection and treatment, leading to improved reporting and reduced mortality and DALYs among infants and young children. However, substantial disparities remain, particularly in lower-income regions with limited access to specialised care. Future efforts should focus on enhancing early detection and expanding access to advanced treatments particularly in LMICs. International collaborations and tailored healthcare policies are essential to bridge treatment gaps, ensuring that all children receive the necessary care to preserve vision and improve survival rates. Improving public awareness and healthcare infrastructure is also crucial for achieving equitable outcomes in the future.

Contributors

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Data sharing statement

The data supporting this study's findings are publicly available from the Institute for Health Metrics and Evaluation website (https://vizhub.healthdata.org/gbd-results).

Editor note

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Declaration of interests

The authors have no conflicts of interest to disclose.

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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.2024.102860.

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