Worldwide burden of liver cancer across childhood and adolescence, 2000–2021: a systematic analysis of the Global Burden of Disease Study 2021

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Summary

Background Liver cancer is a significant contributor to the global disease burden, of which hepatoblastomas are the most common liver tumors in children, with 90% of cases occurring within the first 5 years of life. It is important for pediatricians and subspecialists in pediatric gastroenterology and hepatology to have knowledge of the epidemiology and incidence trends of pediatric hepatic cancer, despite its rarity. In the present study, we first provide estimates of the incidence and mortality burden of hepatoblastoma and liver cancer from 2000 to 2021 in the childhood and adolescence.

Methods Liver cancer burden and its attributable risk factors were estimated using data from the Global Burden of Disease Study (GBD) 2021. Percentage change was estimated to show the trend of liver cancer estimates from 2000 to 2021. The age-standardized rate (ASR) and estimated annual percentage change (EAPC) were utilized for measuring hepatoblastomas incidence and deaths rate trends. In accordance with the GBD framework, 95% uncertainty intervals (UIs) for all estimates by averaging the data from 1000 draws, with the lower and upper bounds of the 95% UIs.

Findings Globally, from 2000 to 2021 in the age 5–19 years group, the incidence cases and deaths cases due to liver cancer decreased from 2449.2 (95% UI: 2235.9–2689.8) to 1692.9 (95% UI: 1482.0–1992.5) and 2248.5 (95% UI: 2053.7–2474.9) to 1516.6 (95% UI: 1322.1–1797.9), respectively. Meanwhile, from 2000 to 2021 in the age 20–24 years group, the incidence cases and deaths cases due to liver cancer decreased from 1453.5 (95% UI: 1327.8–1609.4) to 1285.1 (95% UI: 1159.2–1447.2) and 1432.3 (95% UI: 1307.6–1585.7) to 1195.5 (95% UI: 1066.1–1355.2), respectively. In addition, the prevalence of liver cancer decreased from 41.9% (95% UI: 18.7%–64.7%) to 26.4% (95% UI: 14.2%–39.1%) in the age 5–19 years group, and 46.6% (95% UI: 42.8%–51.5%) to 36.5% (95% UI: 33.1%–40.9%) in the age 20–24 years. From 2000 to 2021, in the age group of 5–19 years, the proportion of liver cancer incidence due to hepatitis B has decreased from 42.2% to 37.9%, while the proportion due to hepatitis C has increased from 1.1% to 1.6%. Additionally, there has been an increase in the proportion of NASH-induced liver cancer incidence from 5.2% to 9.4%, and alcohol use induced liver cancer incidence has also increased from 0.5% to 0.7% over the same period. Globally, from 2000 to 2021, the incidence cases and deaths cases due to hepatoblastoma decreased from 6131.8 (95% UI: 5234.8–6961.9) to 4045.6 (95% UI: 3250–4995.8) and 4059.2 (95% UI: 3494.5–4621.2) to 2416 (95% UI: 1940.2–3022.5), respectively. There was some variation in age-related sex-specific patterns, the highest number of hepatoblastoma incidence cases occurred in children between 2 and 4 years old and females in the age range of 12 months to 9 years had a higher number of new cases. Importantly, the incidence of hepatoblastoma was started to increase sharply after the age of 1 month.

Interpretation The results of the present study are significant for liver health policy and practice in childhood and adolescence. Differentiated intervention and outreach strategies based on age and gender would be necessary to reduce the impact of liver cancer. Early screening and interventions for hepatoblastoma is important especially in the population of under 9 years old.

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Keywords: Liver cancer; Global Burden of Disease Study; Incidence; Hepatoblastoma; Childhood; Adolescence

Research in context

Evidence before this study

Prior research on the burden and risk factors of liver cancer (especially hepatoblastomas) across childhood and adolescence in the global was limited. In order to gather existing evidence, we carried out an extensive search of literature in databases such as PubMed, Web of Science, Cochrane Library, and Embase up to May 2024 with specific terms as part of our strategy: (hepatic carcinoma OR liver cell carcinoma OR liver cell carcinoma OR hepatic cell carcinoma OR hepatocellular carcinoma OR hepatocarcinoma OR hepatoma OR liver carcinoma OR primary liver carcinoma OR HCC OR malignant hepatoma OR carcinoma of the liver OR hepatoblastomas) AND (adolescents OR young adults OR youth) AND (epidemiology OR burden OR prevalence OR risk factors) AND (GBD OR Global Burden of Disease). The purpose of this study is to address the gaps in knowledge by providing estimates of the burden and risk factors for liver cancer in children and adolescents, specifically looking at gender and age categories.

Added value of this study

As part of the GBD 2021 study, this research represents the first utilization of GBD data to systematically evaluate the global disease burden of liver cancer and hepatoblastoma in terms of incidence and mortality across childhood and adolescence from 2000 to 2021. Hepatoblastoma is the only cause of liver cancer in the population of under 9 years old and liver cancer due to hepatitis B and hepatitis C was the mainly risk factor in the age 10–14 years group and people over 15 years old are experiencing an increase in cancer caused by alcohol use and NASH. Particularly noteworthy is that the main reasons for liver cancer related mortality and morbidity varied greatly across regions and NASH-induced liver cancer is increasing dramatically worldwide, especially in the age 15–24 years group.

Implications of all the available evidence

These latest findings offer the most authoritative information on the disease burden of liver cancer among childhood and adolescence, specifically geared towards pediatricians and subspecialists in pediatric gastroenterology and hepatology on a global scale. Policy makers can utilize the data to identify areas for improvement in screening, prevention, and treatment programs. The research also highlights the importance of international collaboration in addressing this global health challenge.

Introduction

Hepatic malignancies, which account for slightly over 1% of all pediatric malignancies, are rare in children. Around 67%–80% of pediatric liver cancers worldwide are hepatoblastoma, with the remaining 20%–33% attributed to hepatocellular carcinoma (HCC).[1] Hepatoblastomas are the most common liver tumors in children, with 90% of cases occurring within the first 5 years of life, while hepatocellular carcinoma is rarely observed in the first 5 years of life, but it becomes the most prevalent malignant liver tumor in older children with more than 65% of cases are found in children over 10 years old.[2] Recent reports have indicated a rise in the occurrence of hepatoblastomas, likely due to the growing population of premature birth survivors and the susceptibility of infants weighing less than 1500 g to develop hepatoblastomas.[3] Hepatocellular carcinoma occurs mostly in older children and adolescents and is typically a result of prolonged liver damage caused by infection with hepatitis B virus (HBV), hepatitis C virus (HCV), alcoholic and non-alcoholic liver disease, or a combination of these factors.[4] The proportion of HCC among pediatric liver cancers varies and depends on the geographical locale and prevalence of these risk factors in the community. Annually, approximately 100–150 new cases of liver tumors are diagnosed in the U.S.[5] HCC is more common among children in South Africa and in regions where there is a high prevalence of HBV infection, such as China, the incidence of HCC is higher compared to hepatoblastoma, which contrasts with findings in Western countries.[6] In the last few decades, the survival rates for liver cancer in children have risen in developed nations, which can be attributed in part to advancements in diagnostic techniques and treatment options.

It is important for pediatricians and subspecialists in pediatric gastroenterology and hepatology to have knowledge about the epidemiology and incidence trends of pediatric hepatic cancer, despite its rare occurrence. This type of cancer might be more commonly observed in certain subgroups, such as mother-to-child HBV transmission and prematurity. Despite the fact that the

cause of hepatoblastoma is mostly unknown, children with a birth weight below 1500 g have been found to have a significantly higher susceptibility to develop hepatoblastoma.[7] Tanimura noted that the minimum age for hepatoblastoma diagnoses tended to be later for children with low birth weight than for children with normal and high birth weights. Tanimura observed that children with low birth weight tended to be diagnosed with hepatoblastoma at a later age compared to children with normal and high birth weights.[8] Due to the inability of current research to assess risk differences between different countries and regions, refining the target population can easily implement liver hepatoblastoma screening. Hepatocellular carcinoma is the most common hepatic malignancy of adolescents. Annually, nearly 2 million new HBV infections occur in children under the age of 5 years.[9] The etiology of hepatocellular carcinoma differs geographically. In western countries, the crucial causes of liver cancer are chronic HCV infection, alcoholism, and nonalcoholic steatohepatitis (NASH). However, in sub-Saharan Africa and most parts of Asia, liver cancer primarily results from chronic HBV infection.[10] The goal of eliminating HBV through universal infant hepatitis B immunisation has made significant advancements, proving highly successful in reducing new cases of infection among children. While children and adolescents with chronic HBV infection have not received as much attention as adults when it comes to testing and treatment strategies, partly due to the lack of strategy in some low-income countries with high HBV prevalence. Thus, quantifying trends and understanding how they vary by country are crucial, which can motivate aetiological research and may provide more powerful evidence for how the incidence rate of liver cancer in children and adolescence changes over time.

Nowadays, the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) study offers a chance to gain a nuanced understanding of hepatoblastoma and liver cancer impacting children and youth. The GBD study not only categorizes age into 5-year intervals but also considers the long-term impact of specific etiologies in the countries and regions worldwide. In the present study, using data from GBD 2021, we first provide estimates of the incidence and mortality burden of hepatoblastoma and liver cancer from 2000 to 2021 in the childhood and adolescence.

Methods

GBD source

The 2021 GBD study provides a detailed evaluation of the health impacts of 369 diseases, injuries, and impairments, along with 88 risk factors, across 204 countries and territories. This analysis is based on the latest epidemiological data and improved standardized techniques. Data download from the Global Health Data Exchange query tool (http://ghdx.healthdata.org/gbd-results-tool), categorized by region, sex, country, and risks. Data on liver cancer from 6040 sources were included in GBD 2021 (https://ghdx.healthdata.org/gbd-2021/sources). The world was also divided into 27 geographical regions.[11] The age-standardized rate (ASR) and estimated annual percentage change (EAPC) were utilized for measuring hepatoblastomas incidence and deaths rate trends.[12] ASR trend was employed for more accurately portraying changes in disease patterns within the population and developing specific preventive strategies for hepatoblastomas. EAPC summary was used for quantifying ASR trends among various populations over a certain period of time.[13] The Socio Demographic Index (SDI) is a comprehensive indicator used to measure the socio-economic, demographic, and developmental levels of different countries and regions. It is calculated based on factors such as per capita gross domestic product (GDP), education level, and total fertility rate for each country or region. The value range of SDI is usually between 0 and 1, with higher values indicating higher levels of socio-economic, demographic, and development in the region, and vice versa indicating lower levels. The 204 countries and territories were divided based on their SDI into five groups: low-SDI, low-middle-SDI, middle-SDI, high-middle-SDI, and high-SDI quintile. By comparing the SDI values of different countries and regions, researchers and policymakers can better understand the overall development and health status of different regions. In addition, individuals were assessed for liver cancer using the International Classification of Diseases (ICD) versions 9 and 10 codes. These codes included 155–155.9 and V10.07 from ICD-9, as well as C22–C22.4 and C22.7-C22.8 from ICD-10. The current GBD estimation is based on the methodology described in the latest GBD study, with more information available elsewhere; a brief overview is given below.[14–16]

Estimates

The GBD 2021 Collaborators[17] modeled incidence and deaths estimates for male and female participants across four age groups: 5–9 years, 10–14 years, 15–19 years, and 20–24 years. Due to hepatoblastomas being included in the GBD 2021 study for the first time, in order to comprehensively evaluate the burden caused by hepatoblastomas in childhood, we also included 0–6 days, 7–27 days, 1–5 months, 6–11 months, 12–23 months, and 2–4 years in the study. Due to the fact that the GBD study does not currently offer combined data for individuals aged 5–24 years old, we thus determined the liver cancer morbidity rate for a wider age range by averaging estimates for different age groups, with the weighting based on the population of each age group worldwide. Meanwhile, we also shown the incidence rate data of liver cancer in the 5–19 years group. The Cause of Death Ensemble model (CODEm) was applied

to estimate cause-specific mortality for each combination of sex, age, location, and year. The GBD team developed the DisMod-MR 2.1 software, a Bayesian meta-regression tool, to conduct incidence estimations through an analytical cascade process. Before conducting the actual modeling, adjusted data points and biases by: (1) disaggregating data that were not already disaggregated into age and sex using age-sex and sex splits, and (2) utilizing a Meta-Regression—Bayesian, Regularized, Trimmed (MR-BRT) model to directly compare study designs and case definitions. Information about bias correction and other adjustments made for each specific disorder can be found in the GBD 2019 capstone report.[18] Additionally, we estimated mortality and disability-adjusted life-years (DALYs) attributed to Level 2 risk factors (alcohol use and drug use) and Level 4 risk factors (high body–mass index). The risk factors were chosen according to the criteria established by the World Cancer Research Fund for strong evidence of risk-outcome connections, as well as the comparative risk assessment framework. Additional details on specific risk methodologies are outlined in the 2021 GBD risk factors capstone.[15]

Statistical analysis

In accordance with the GBD framework, 95% uncertainty intervals (UIs) for all estimates by averaging the data from 1000 draws with replacement, with the lower and upper bounds of the 95% UIs determined by the 25th and 95th ranked values among all 1000 draws.[18] In GBD, a large number of simulations are typically used to estimate uncertainty and other statistical indicators. A sample size of 1000 is considered sufficient in many cases, especially when the sample size is large and the population distribution is close to a normal distribution. ASR and EAPC were calculated following Liu et al.'s method.[19] It was found that both the EAPC value and the upper boundary of the 95% CI were less than zero, indicating a decreasing trend in ASR. Conversely, the EAPC value and the lower boundary of the 95% CI were greater than zero, suggesting a rising trend in ASR. A 95% CI of 0 signifies a stable trend in ASR. Incidence rates were adjusted for age to the 2000 US standard population and reported per 100,000 person-years. The database and scripts (packages) used to perform the analysis can be found in Supplementary Table S1 and S2. All statistical analyses were carried out using R software (R 4.2.3).

Role of the funding source

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. All authors had full access to the dataset. The corresponding authors had final responsibility for the decision to submit for publication.

Results

Global liver cancer burden

The study flowchart was shown in Fig. 1. Globally, from 2000 to 2021 in the age 5–19 years group, the incidence cases and deaths cases due to liver cancer decreased from 2449.2 (95% UI: 2235.9–2689.8) to 1692.9 (95% UI: 1482.0–1992.5) and 2248.5 (95% UI: 2053.7–2474.9) to 1516.6 (95% UI: 1322.1–1797.9), respectively. Meanwhile, from 2000 to 2021 in the age 20–24 years group, the incidence cases and deaths cases due to liver cancer decreased from 1453.5 (95% UI: 1327.8–1609.4) to 1285.1 (95% UI: 1159.2–1447.2) and 1432.3 (95% UI: 1307.6–1585.7) to 1195.5 (95% UI: 1066.1–1355.2), respectively. In addition, the prevalence of liver cancer decreased from 41.9% (95% UI: 18.7%–64.7%) to 26.4% (95% UI: 14.2%–39.1%) in the age 5–19 years group, and 46.6% (95% UI: 42.8%–51.5%) to 36.5% (95% UI:

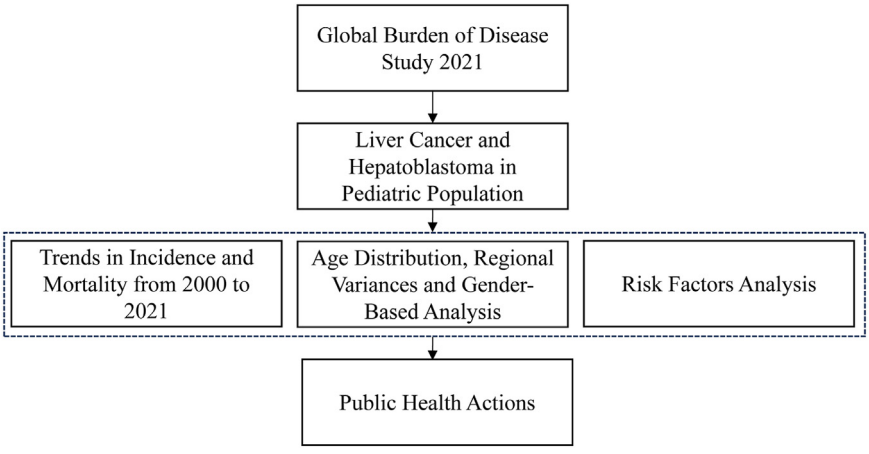

Fig. 1: The study flowchart of worldwide burden of liver cancer across childhood and adolescence from 2000 to 2021.

33.1%–40.9%) in the age 20–24 years. As anticipated, significant disparities were noted among the age subgroups for both individuals, with the morbidity of liver cancer in the age 20–24 years group (21.52%; 95% UI, 19.41–24.23) estimated at approximately 3 times that recorded for the age 5–9 years group (8.28%; 95% UI, 7.02–9.96). The steep increase in liver cancer across age subgroups is particularly striking due to the specific etiologies. In the age 5–9 years group, hepatoblastoma is the only cause of liver cancer, which can even extend to the entire population under 9 years old. Liver cancer due to hepatitis B and hepatitis C was the mainly risk factor in the age 10–14 years group and people over 15 years old are experiencing an increase in cancer caused by alcohol use and NASH. Importantly, there was some variation in age-related sex-specific patterns, as male children and youths shown higher morbidity liver cancer due to hepatitis B. For liver cancer due to hepatitis C and NASH, the number of females cases is higher than that of males, while for liver cancer due to hepatitis B and alcohol use, the number of males cases is higher than that of females. For liver cancer due to hepatoblastoma, the sex ratios were more balanced Table 1 and Fig. 2.

From 2000 to 2021, in the age group of 5–19 years, the proportion of liver cancer incidence due to hepatitis B has decreased from 42.2% to 37.9%, while the proportion due to hepatitis C has increased from 1.1% to 1.6%. Additionally, there has been an increase in the proportion of NASH-induced liver cancer incidence from 5.2% to 9.4%, and alcohol use induced liver cancer incidence has also increased from 0.5% to 0.7% over the same period Fig. 3. Most notably, the proportion of liver cancer incidence due to hepatoblastoma has decreased from 37.6% to 33.6%. Similar trends were observed in the proportion of liver cancer deaths caused by specific etiologies Supplementary Fig. S1.

Liver cancer due to hepatoblastoma burden

As hepatoblastoma is the only cause of liver cancer in the population of under 9 years old, thus, we have conducted a detailed estimate of the burden caused by hepatoblastoma. Globally, from 2000 to 2021, the

Cause	Incidence rate, % (95% UI)				
	Age 5–9 y	Age 10–14 y	Age 15–19 y	Age 20–24 y	Age 5–19 y
Liver cancer					
Total	8.28 (7.02–9.96)	4.82 (3.91–5.92)	12.86 (11.23–14.96)	21.52 (19.41–24.23)	8.56 (7.49–10.07)
Female	8.17 (6.75–9.97)	4.28 (3.33–5.55)	13.06 (11.01–15.62)	17.48 (15.41–20.00)	8.41 (7.19–10.12)
Male	8.39 (7.04–10.38)	5.33 (4.35–6.71)	12.68 (11.06–14.90)	25.43 (22.66–30.11)	8.71 (7.56–10.27)
Liver cancer due to hepatitis B					
Total	NA	3.09 (2.44–3.94)	7.00 (5.78–8.52)	13.80 (11.93–16.17)	3.24 (2.66–4.00)
Female	NA	2.06 (1.51–2.81)	5.14 (3.90–6.74)	8.29 (6.74–10.24)	2.32 (1.75–3.04)
Male	NA	4.05 (3.23–5.27)	8.74 (7.31–10.57)	19.13 (16.46–23.25)	4.12 (3.44–5.02)
Liver cancer due to hepatitis C					
Total	NA	0.13 (0.07–0.20)	0.29 (0.15–0.48)	0.80 (0.51–1.21)	0.13 (0.07–0.22)
Female	NA	0.14 (0.08–0.24)	0.37 (0.19–0.62)	1.00 (0.62–1.53)	0.17 (0.09–0.28)
Male	NA	0.11 (0.06–0.17)	0.21 (0.11–0.36)	0.62 (0.37–1.00)	0.10 (0.05–0.17)
Liver cancer due to alcohol use					
Total	NA	NA	0.19 (0.08–0.35)	0.88 (0.57–1.35)	0.06 (0.03–0.11)
Female	NA	NA	0.16 (0.07–0.31)	0.61 (0.39–0.92)	0.05 (0.02–0.10)
Male	NA	NA	0.21 (0.09–0.40)	1.15 (0.75–1.77)	0.07 (0.03–0.12)
Hepatoblastoma					
Total	8.28 (7.02–9.96)	NA	NA	NA	2.88 (2.44–3.46)
Female	8.17 (6.75–9.97)	NA	NA	NA	2.83 (2.34–3.46)
Male	8.39 (7.04–10.38)	NA	NA	NA	2.92 (2.45–3.61)
Liver cancer due to NASH					
Total	NA	NA	2.54 (1.79–3.41)	2.85 (2.08–3.82)	0.80 (0.56–1.08)
Female	NA	NA	3.49 (2.45–4.76)	3.60 (2.61–4.75)	1.10 (0.78–0.51)
Male	NA	NA	1.64 (1.13–2.30)	2.12 (1.51–2.99)	0.52 (0.36–0.72)
Liver cancer due to other causes					
Total	NA	NA	2.86 (2.04–3.84)	3.19 (2.36–4.20)	1.44 (1.06–1.90)
Female	NA	NA	3.89 (2.75–5.20)	3.99 (2.94–5.20)	1.93 (1.40–2.58)
Male	NA	NA	1.88 (1.32–2.56)	2.42 (1.74–3.27)	0.99 (0.71–1.33)

NA: not applicable; UI: uncertainty interval.

Table 1: **Global incidence rate of liver cancer among children and youths in 2021.**

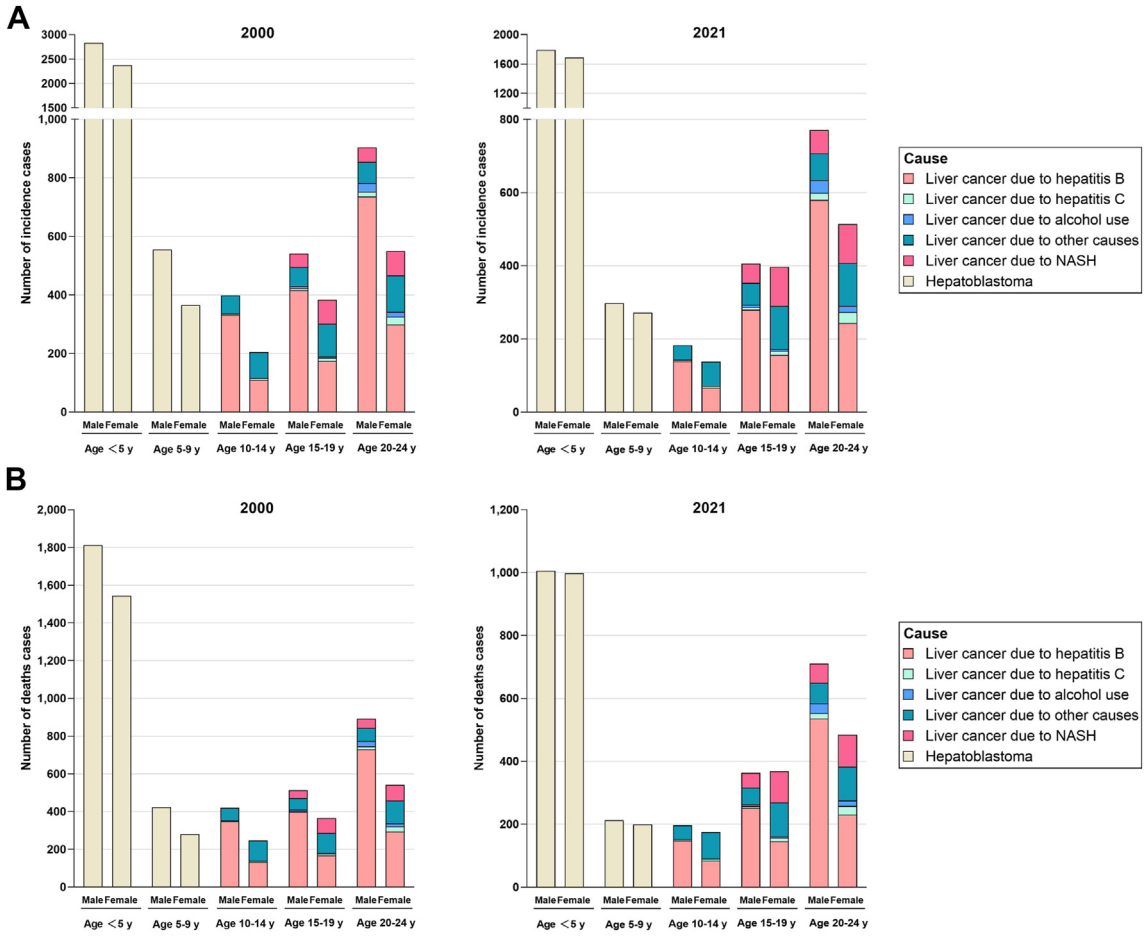

Fig. 2: The contribution of specific etiologies (liver cancer due to hepatitis B, hepatitis C, alcohol use, nonalcoholic steatohepatitis (NASH), hepatoblastoma, and other causes) in different age groups among children and youths in 2000 and 2021. A. Incidence cases; B. Deaths cases.

incidence cases and deaths cases due to hepatoblastoma decreased from 6131.8 (95% UI: 5234.8–6961.9) to 4045.6 (95% UI: 3250–4995.8) and 4059.2 (95% UI: 3494.5–4621.2) to 2416 (95% UI: 1940.2–3022.5), respectively. The morbidity and mortality rate in most areas showed a downward trend, except for Australasia and High-income North America. Although the growth trend of ASIR in Australasia and High-income North

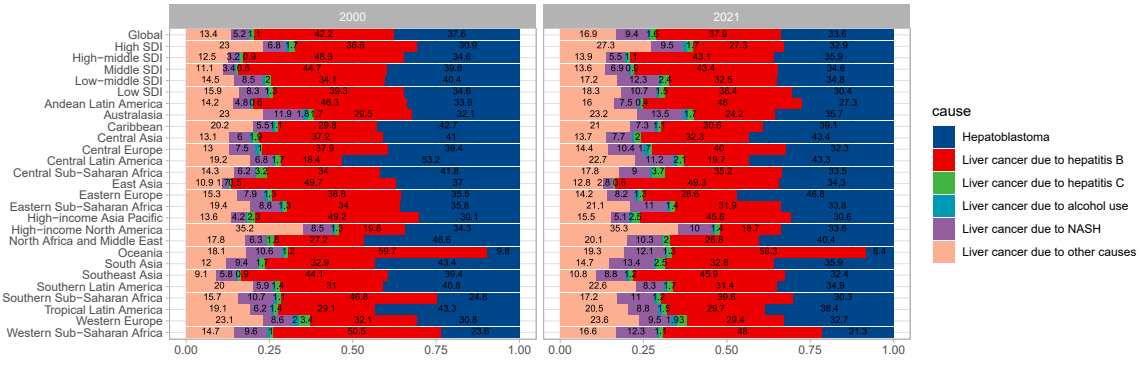

Fig. 3: The incidence rate of contribution of specific etiologies (liver cancer due to hepatitis B, hepatitis C, alcohol use, nonalcoholic steatohepatitis (NASH), hepatoblastoma, and other causes) in different regions in the age group of 5–19 years in 2000 and 2021. SDI, socio demographic index.

America was consistent, the growth of ASDR in Australasia is about twice that of High-income North America Table 2. In the Australasia, ASIR and ASDR increased by an average of 1.63% (95% CI 1.18%–2.09%) per year (from 8.6 per 100,000 in 2000 to 2.09 per 100,000 in 2021) and 1.23% (95% CI 0.79%–1.68%) per year (from 2.2 per 100,000 in 2000 to 3.1 per 100,000 in 2021), respectively. Observed downward trend of deaths EAPC was highest in East Asia (–6.8) and the minimum was Caribbean (–0.52) Table 2. Moreover, Mali had the highest observed ASIR (36.0 per 100,000 in 2021), followed by Gambia (28.2 per 100,000 in 2021), as shown in Fig. 4. Similar trends were also observed in ASDR Supplementary Fig. S2. At the national level for incidence cases, Cook Islands had the highest observed decreased EAPC (–7.18, 95% CI: –7.99 to –6.36), followed by Mauritius (–6, 95% CI: –7.10 to –4.88) and Poland had the highest observed increased EAPC (4.76, 95% CI: 3.83–5.69), followed by Belarus (4.71, 95% CI: 3.15–6.29) Supplementary Table S3. Similarly, for deaths cases, Cook Islands had the highest observed decreased EAPC (–7.97, 95% CI: –8.74 to –7.19), followed by Singapore (–6.97, 95% CI: –7.89 to –6.04) and Dominica had the highest observed increased EAPC (3.54, 95% CI: 2.8–4.29), followed by Norway (3.45, 95% CI: 1.81–5.12) Supplementary Table S4. There was some variation in age-related sex-specific patterns, the highest number of incidence cases occurred in children between 2 and 4 years old and females in the age range of 12 months to 9 years had a higher number of new cases. Importantly, the incidence of hepatoblastoma was started to increase sharply after the age of 1 month Fig. 5 and Table 3.

Liver cancer burden by risk factors

Due to the higher exposure to risk factors in the age groups of 15–19 years and 20–24 years, we have therefore characterized the attribution of risk factors to the deaths and DALYs in these two age groups in 2021. In the age group of 15–19 years for high alcohol use, the deaths proportion in Southern Latin America (8.2%) and Western Europe (8.1%) was the highest and for drug use, the proportion in High–income North America (19.6%) and Eastern Europe (15.4%) was the highest Supplementary Fig. S3. In the 15 to 19 age group, the male mortality attributable to alcohol use and drug use was greater than that of female. Notably, drug use was largely concentrated in the America and Europe region, for example, Eastern Europe (Male: 23.8% vs Female: 7.4%) and High–income North America (Male: 24.7% vs Female: 13.4%) have 3.22-fold and 1.84-fold for male when compared to female. Whereas, drug use was low in the Asia and Africa, such as Western Sub-Saharan African (Male: 0.2% vs Female: 0.2%) and

Location	2000		2021		2000–2021	2000–2021
	Incident cases No. (95% UI)	Deaths cases No. (95% UI)	Incident cases No. (95% UI)	Deaths cases No. (95% UI)	Incident EAPC (95% CI)	Deaths EAPC (95% CI)
Global	6131.8 (5234.8–6961.9)	4059.2 (3494.5–4621.2)	4045.6 (3250–4995.8)	2416 (1940.2–3022.5)	–1.82 (–2.01 to 1.62)	–2.38 (–2.57 to 2.19)
Andean Latin America	25.9 (20–33.7)	17.9 (13.9–23.1)	15.5 (10.4–22.4)	9.9 (6.8–14.4)	–2.82 (–3.19 to 2.44)	–3.24 (–3.58 to 2.9)
Australasia	8.6 (7.6–9.8)	2.2 (2–2.5)	13.3 (10.4–16.6)	3.1 (2.5–3.8)	1.63 (1.18–2.09)	1.23 (0.79–1.68)
Caribbean	8.7 (6.6–12.3)	6 (4.4–8.6)	7.1 (4.7–11)	4.8 (3.1–7.5)	–0.46 (–0.6 to 0.31)	–0.52 (–0.68 to 0.37)
Central Asia	65.1 (51–83)	45.6 (35.7–57.6)	42.4 (31–56.8)	28.1 (21–37.2)	–2.9 (–3.13 to 2.67)	–3.17 (–3.4 to 2.94)
Central Europe	17.9 (15.6–20.7)	10.7 (9.2–12.5)	8.9 (7.2–11)	3.5 (2.9–4.4)	–2.02 (–2.38 to 1.66)	–4.11 (–4.49 to 3.72)
Central Latin America	134.7 (122.7–149.1)	90.8 (81.9–100.6)	86.2 (66.4–112.9)	55 (42.1–71.5)	–1.19 (–1.35 to 1.02)	–1.49 (–1.65 to 1.34)
Central Sub-Saharan Africa	161 (92.2–264)	114.5 (64.7–187.3)	96.5 (43.1–177.1)	67.9 (31–126.2)	–4.21 (–4.42 to 4)	–4.27 (–4.48 to 4.06)
East Asia	1764.4 (1510.6–2054.3)	1181.6 (1015.6–1353.4)	565.8 (401.6–801.9)	221.6 (161.2–309)	–3.96 (–4.59 to 3.32)	–6.8 (–7.3 to 6.3)
Eastern Europe	68.7 (65.4–72.1)	43.3 (41.1–45.8)	58.8 (53.1–64.3)	26 (23.5–28.5)	–0.46 (–1.24 to 0.34)	–2.64 (–3.18 to 2.1)
Eastern Sub-Saharan Africa	607.9 (451.5–800.9)	429.6 (318.7–576.6)	509.8 (296.9–887.7)	356.1 (212.4–618.2)	–1.95 (–2.14 to 1.76)	–2.02 (–2.21 to 1.83)
High-income Asia Pacific	119.5 (110.8–129.7)	37.3 (33.9–41.3)	37.6 (33.1–44.5)	8.5 (7.6–9.9)	–4.05 (–4.66 to 3.45)	–5.57 (–5.84 to 5.3)
High-income North America	149.7 (146–153.4)	41.7 (40.8–42.7)	179.2 (159.5–200.1)	44.7 (40–49.5)	1.27 (1–1.53)	0.79 (0.6–0.98)
High-middle SDI	785.8 (691.6–897.9)	493.9 (431.2–563.7)	359.6 (290–448.1)	131.3 (109–158.9)	–2.54 (–3.11 to 1.97)	–5.56 (–6.12 to 5)
High SDI	389.1 (375.1–403.5)	122.2 (116.7–128.4)	345 (314.7–374)	85.2 (78.1–91.8)	–0.21 (–0.42 to 0)	–1.3 (–1.41 to 1.19)
Low-middle SDI	1445 (1092–1796.3)	1015.1 (753.8–1260.5)	1102 (886.3–1345.3)	752.2 (605.7–936.9)	–1.18 (–1.32 to 1.04)	–1.34 (–1.49 to 1.18)
Low SDI	1568.1 (1185.7–1919.4)	1107 (839.9–1366.5)	1416.6 (996.2–1916.9)	987.2 (708.1–1332.6)	–1.81 (–1.98 to 1.65)	–1.88 (–2.05 to 1.72)
Middle SDI	1933.8 (1708.6–2160.2)	1319.6 (1174–1467.2)	823.5 (655.8–1044)	458.8 (368.5–579.7)	–3.1 (–3.55 to 2.65)	–4.19 (–4.58 to 3.81)
North Africa and Middle East	395.7 (326.5–477.3)	271.7 (223.9–332.5)	329.2 (258.3–418.2)	208 (162.4–272.3)	–1.19 (–1.38 to 1)	–1.64 (–1.83 to 1.44)
Oceania	3.9 (2.5–6.3)	2.7 (1.7–4.3)	4 (2.3–7.1)	2.8 (1.6–5)	–2.41 (–2.68 to 2.13)	–2.44 (–2.72 to 2.17)
South Asia	1053.6 (681.7–1405.7)	743 (467.6–981)	815.5 (632.7–1044.5)	559.4 (430.2–722.8)	–0.73 (–0.86 to 0.61)	–0.89 (–1.02 to 0.76)
Southeast Asia	448.7 (352.4–552.9)	309 (240.1–383.2)	252.4 (185.7–346.6)	163.8 (121.1–226)	–2.34 (–2.46 to 2.23)	–2.66 (–2.76 to 2.55)

EAPC: estimated annual percentage change; CI: confidence interval; UI: uncertainty interval.

Table 2: **The age-standardized rate and temporal trends of hepatoblastoma in 2000 and 2021.**

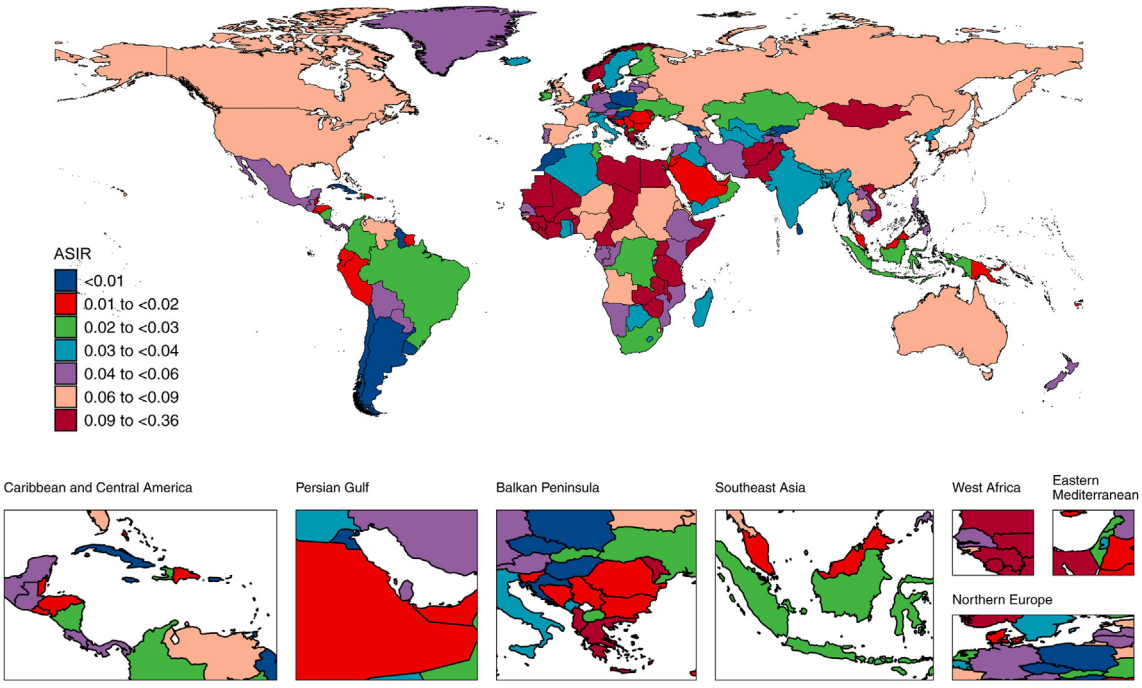

Fig. 4: The age-standardized incidence rate (ASIR) of liver cancer in countries and territories in 2021.

South Asia (Male: 2.1% vs Female: 1.2%). Liver cancer burden attributable to high body–mass index (BMI) starts to increase in 20–24 years group. In the age group of 20–24 years for high alcohol use, the proportion in Australasia (12.9%) and Western Europe (13.9%) was the highest and the percentage of male mortality was generally about twice that of female in 27 regions. As for drug use, the proportion in High–income North America (27.5%) and Australasia (17.3%) was the highest and the percentage of male was higher when compared to female except for Tropical Latin American (Male: 10.1% vs Female: 11.3%). Moreover, the percentage of female mortality was higher when compared to male attributable to high BMI, while in South Asia, East Asia, High-income Asia Pacific, and Central Europe, the percentage of male mortality was higher when compared to female Supplementary Fig. S4. In summary, late adolescence is particularly striking in High–income North America, Europe, and Australasia for alcohol and drug use. At the same time, the challenges brought by BMI should be strengthened. The trend of DALYs changes is consistent with deaths. This reflects the importance of considering the impact of gender differences in different regions when formulating risk factor strategies.

Discussion

The current study outlines the global morbidity and mortality rates of liver cancer in children and young adults, based on their stage of development and gender based on the GBD 2021 study. From 2000 to 2021, there was a consistent decline in the occurrence and death rates of liver cancer on a global scale in the age 5–19 years group. Hepatoblastoma is the only cause of liver cancer in the population of under 9 years old and liver cancer due to hepatitis B and hepatitis C was the mainly risk factor in the age 10–14 years group and people over 15 years old are experiencing an increase in cancer caused by alcohol use and NASH. It is also worth noting that the main reasons for liver cancer related mortality and morbidity varied greatly across regions and NASH-induced liver cancer is increasing dramatically worldwide, especially in the age 15–24 years group.

GBD gives us the opportunity to provide an overview of hepatoblastoma's disease burden for the first time. In our study, we found that the morbidity and mortality rate in most areas showed a downward trend, except for Australasia and High-income North America. Until now, only a few population-based studies have reported the trends in hepatoblastoma incidence over the past few decades. From 1975–1979 to 1990–1995, the rate of hepatoblastoma cases nearly doubled from 0.8 per million to 1.5 per million over a span of 21 years based on The Surveillance, Epidemiology and End Results (SEER) program, which mainly including American childhood.[20] Although, in 1972, the first cooperative study in North America was initiated to treat children with malignant liver tumors by members of the Children's Cancer Study Group (CCSG) and the Pediatric

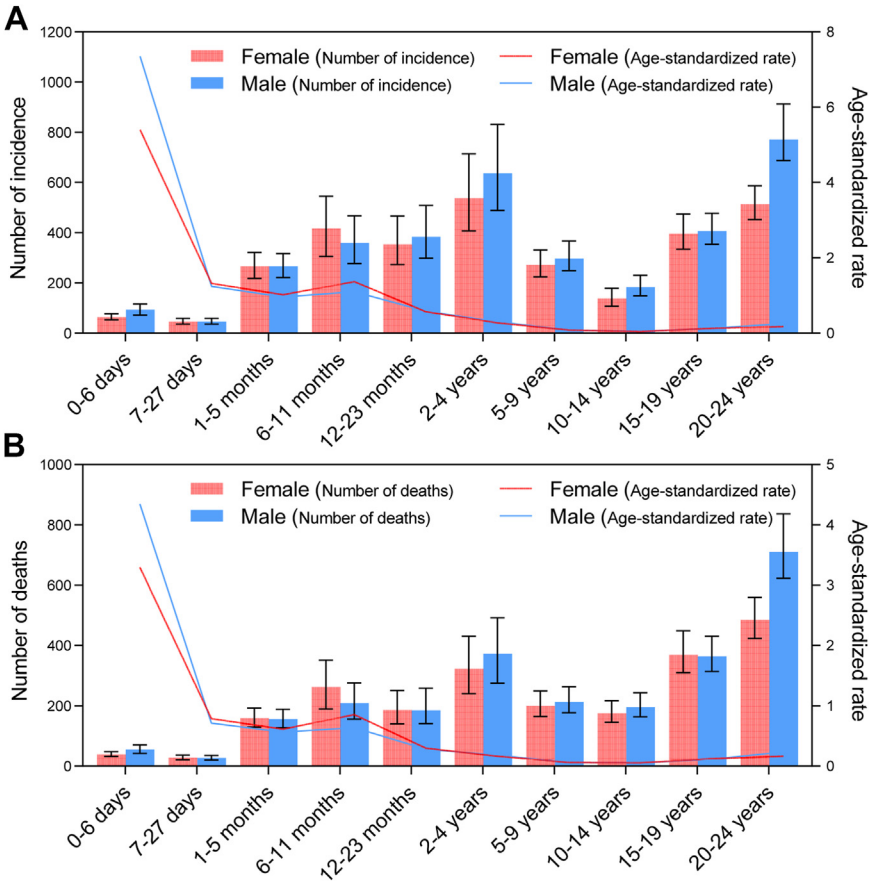

Fig. 5: The incidence of hepatoblastoma in the different age groups in global 2021. A. Number of incidence and age-standardized incidence rate; B. Number of deaths and age-standardized deaths rate.

Division of the Southwest Oncology Group (SWOG).[21] The Taiwan Cancer Registry (TCR) database was analyzed in a recent population-based study which found that from 1995 to 2012, there was a 7.4% yearly increase in the overall incidence of hepatoblastoma in children, with a specific 6.5% increase among males.[22] While epidemiological studies may reveal important factors related to the cause of hepatic tumors in children for the eradication of these tumors. A recent study indicated that surgery, ethnicity, and age were identified as independent prognostic factors, however, there is still a lack of global data.[23] The incidence of hepatoblastoma increased by 2.3% between 1983 and 2015 in Australasia childhood,[24] although the reasons for the rises are largely unknown, while more health service is needed for children. Moreover, a majority of hepatoblastoma cases occur between the ages of 6 months and 3 years,[25] which is consistent with our findings, the highest number of incidence cases occurred in children between 2 and 4 years old. But the difference in gender ratio (1.18) is more pronounced in 2 and 4 years old which is lower of data from group trials in the U.S. and Europe.[26] Incorporating a stronger focus on primary prevention is critical for comprehensive strategies to reduce the incidence and impact of hepatoblastoma in children. Highlight the major risk factors associated with hepatoblastoma, such as low birth weight, prematurity, genetic conditions (like Beckwith-Wiedemann syndrome), and familial predisposition.[27] Furthermore, stress the significance of health education and awareness campaigns targeting healthcare providers, parents, and communities to promote early detection, prompt referral, and timely treatment of hepatoblastoma. In summary, these data demonstrate the importance of conducting detailed analyses throughout childhood and adolescence, which could be benefit for care and prevention efforts.

Liver cancer due to HBV infection was still the mainly risk factor in the developmental stages of early adolescence, late adolescence, and early adulthood. HBsAg carriage is common in Asia, Africa, Southern Europe, and Latin America, with prevalence rates ranging from 2% to 20% in the general population.[28] The WHO Africa Region has the highest prevalence of

Age group	Incidence number, % (95% UI)	Incidence ASR, % (95% UI)	Deaths number, % (95% UI)	Deaths ASR, % (95% UI)
0–6 days				
Total	157.22 (191.2, 129.76)	6.41 (7.8, 5.29)	94.13 (115.72, 77.17)	3.84 (4.72, 3.15)
Female	63.96 (77.32, 53.41)	5.4 (6.53, 4.51)	39.05 (48, 32.51)	3.3 (4.06, 2.75)
Male	93.26 (116.82, 72.63)	7.36 (9.22, 5.73)	55.09 (70.41, 42.41)	4.35 (5.55, 3.35)
7–27 days				
Total	93.56 (118.2, 74.4)	1.28 (1.62, 1.02)	54.77 (70.44, 42.9)	0.75 (0.97, 0.59)
Female	46.72 (59.69, 36.62)	1.33 (1.69, 1.04)	27.9 (36.36, 21.44)	0.79 (1.03, 0.61)
Male	46.84 (59.31, 36.94)	1.24 (1.57, 0.98)	26.88 (35.07, 20.88)	0.71 (0.93, 0.55)
1–5 months				
Total	533.56 (623.88, 446.33)	0.99 (1.16, 0.83)	315.83 (371.02, 261.58)	0.59 (0.69, 0.49)
Female	266.82 (321.95, 218.4)	1.03 (1.24, 0.84)	159.65 (194.12, 129.01)	0.61 (0.75, 0.5)
Male	266.74 (317.66, 221.74)	0.96 (1.14, 0.8)	156.18 (187.34, 127.28)	0.56 (0.67, 0.46)
6–11 months				
Total	778.76 (1004.06, 590.21)	1.23 (1.59, 0.93)	471.76 (614.12, 354.28)	0.75 (0.97, 0.56)
Female	417.8 (545.45, 305.59)	1.37 (1.79, 1)	262.34 (346.2, 188.85)	0.86 (1.13, 0.62)
Male	360.96 (467.83, 277.55)	1.11 (1.43, 0.85)	209.41 (272.59, 156.69)	0.64 (0.83, 0.48)
12–23 months				
Total	741.89 (959.26, 585.32)	0.58 (0.75, 0.46)	371.19 (491.51, 282.58)	0.29 (0.38, 0.22)
Female	355.59 (466.86, 273.65)	0.57 (0.75, 0.44)	186.15 (252.44, 139.63)	0.3 (0.41, 0.22)
Male	386.3 (510.88, 299.94)	0.58 (0.77, 0.45)	185.04 (252.65, 138.78)	0.28 (0.38, 0.21)
2–4 years				
Total	1174.29 (1496.27, 904.96)	0.29 (0.37, 0.22)	696.64 (904.2, 528.85)	0.17 (0.22, 0.13)
Female	537.73 (714.37, 407.41)	0.28 (0.37, 0.21)	323.28 (434.25, 240.54)	0.17 (0.22, 0.12)
Male	636.56 (831.9, 488.18)	0.31 (0.4, 0.23)	373.35 (498, 277.64)	0.18 (0.24, 0.13)

NA: not applicable; ASR: age-standardized rate; UI: uncertainty interval.

Table 3: **Global incidence and deaths of hepatoblastoma among age subgroups in 2021.**

HBsAg in children and adults, with only 10% receiving timely birth-dose vaccination within 24 h of birth.[29] In western Europe and North America, HBsAg positivity in individuals under 18 is uncommon. Nonetheless, there is a growing number of children with HBV infection migrating to these regions from countries with higher prevalence rates.[30] Male children and youths shown higher morbidity liver cancer due to HBV. Depending on the age at which it is acquired, childhood HBV infection can have different natural histories and long-term outcomes. The risk of developing chronic HBV infection is lower at 30% when the infection occurs in the first 5 years of life and less than 5% for older immunocompetent children and adults. The universal vaccination of newborns has led to a decrease in the incidence of HCC from childhood to early adulthood. The majority of HCC cases that are not prevented well from the inability to effectively control HBV infection from highly infectious mothers. In Japan, many individuals with chronic HBV infection stop visiting medical facilities during adolescence or young adulthood due to insufficient awareness of the potential morbidities and complications associated with the infection. It is crucial to ensure that young patients who acquire HBV infection in childhood receive continuous care. While the importance of transmission routes for HBV may differ in various countries, it is still recommended that universal hepatitis B vaccination for infants be implemented in all countries, regardless of the prevalence of HBV.

Liver cancer due to HCV shows a slow growth trend in almost all regions around the world, but the deaths cases decreased by 0.2% in region Western Europe. Interestingly, liver cancer due to NASH is increasing at a relatively noticeable tread in the global, as it has increased 4% in twenty years from 2000 to 2021. Testing, treatment, and preventive strategies for children and adolescents have received less focus compared to adults partly due to the lack of approval for direct-acting antiviral regimens in individuals under 18 until 2017.[31] Thus, strategies to promote the scale-up of testing and treatment in childhood and adolescence is needed. NASH, as a severe form of non-alcoholic fatty liver disease (NAFLD), while due to variations in diagnosis methods and inconsistent definitions of obesity in childhood, it is challenging to accurately determine the prevalence of NAFLD in children and adolescents. In the Study of Child and Adolescent Liver Epidemiology in the USA, 9.6% of children and adolescents aged 2–19 years were found to have histologically confirmed NAFLD in autopsy samples and among obese children, the prevalence of fatty liver increased to 38%.[32] Nobili

and colleagues conducted a study to determine the prevalence of paediatric NAFLD, finding the highest rates in Central America and the Middle East. They reported that 42.5% of children aged 8–11 in Mexico had elevated alanine aminotransferase (ALT) levels, while 16.9% of children aged 6–19 in Iran showed signs of NAFLD on ultrasound.[33] Prevalence estimates of obesity in adolescents were found to be lower in clinical studies conducted in South America and higher in studies conducted in Asia compared to those in Europe, Middle East/North Africa, and North America.[34] In our study, we found that the highest prevalence of liver cancer due to NASH was Australasia (2.8%), followed by Southern Sub-Saharan Africa (2.6%) and Western Sub-Saharan Africa (2.4%) in the 5–19 years old group. Meanwhile, the highest prevalence of liver cancer due to NASH was Southern Sub-Saharan Africa (6.4%), followed by Australasia (5.6%) and High-income North America (4.5%) in the 20–24 years old group. Epidemiological data are crucial in order to fully comprehend the impact of NAFLD on healthcare systems, considering its link to both hepatic and extrahepatic manifestations. In addition, national implementing policies that promote healthy environments and lifestyles to prevent obesity and metabolic disorders, which are major risk factors for NAFLD.[32] These may include regulations on food advertising, school meal programs, urban design promoting physical activity, and taxation of sugary beverages.[35–37]

Some limitations of our study must be acknowledged. First, there are limited data sources in developing regions and populations, necessitating epidemiological studies that concentrate on standardized age groups. Second, as GBD data does not currently support tracking multimorbidity, we were unable to measure co-occurring disorders and the burden of common risk factors and dietary patterns. Finally, due to the specific etiologies in different regions, when interpreting the findings, readers should consider the perspectives of informants in different age groups and regions when interpreting the results to ensure a comprehensive understanding of the disease patterns and trends. Continued research and targeted interventions are essential to further reduce the burden of liver cancer and hepatoblastoma in this vulnerable population. Future research should focus on expanding data collection efforts in developing regions and populations, as well as incorporating more standardized age groups and multimorbidity tracking. This will help improve the accuracy and generalizability of epidemiological studies on liver cancer in children and young adults, ultimately informing more effective public health interventions. Moreover, efforts should be made to strengthen surveillance infrastructure in regions with limited healthcare resources to enhance disease tracking and early detection of liver cancer cases. Collaboration between international organizations, governments, and local healthcare providers is essential to build robust surveillance systems and ensure timely reporting of data. Focus on Region-Specific Analyses: To address the challenges posed by regional variances in liver cancer risk factors and etiologies, future research should prioritize region-specific analyses. By tailoring interventions to the specific needs of different geographic areas, healthcare providers can better address the unique challenges of liver cancer prevention and management in diverse populations. The results of the present study are significant for liver health policy and practice in childhood and adolescence. Differentiated intervention and outreach strategies based on age and gender would be necessary to reduce the impact of liver cancer. The government should focus on early identification of NAFLD patients and prioritize intensive lifestyle modification interventions. Early screening and interventions for hepatoblastoma is important especially in the population of under 9 years old.

Contributors

W.Z.H. and X.F.N. designed and analyzed the research study; Z.K., F.M.K, and W.W.J. collected the data; X.F.N. validation and visualisation the data. W.Z.H. and L.R. wrote and revised the manuscript. All authors have read and approved the manuscript.

Data sharing statement

The data from this study can be accessed openly through the GBD 2021 online database, as outlined in the Methods section.

Editor note

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Declaration of interests

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102765.

References

1 Ranganathan S, Lopez-Terrada D, Alaggio R. Hepatoblastoma and pediatric hepatocellular carcinoma: an update. *Pediatr Dev Pathol*. 2020;23(2):79–95.
2 Dezsőfi A, McLin V, Hadzic N. Hepatic neoplasms in children: a focus on differential diagnosis. *Clin Res Hepatol Gastroenterol*. 2014;38(4):399–402.
3 Khanna R, Verma SK. Pediatric hepatocellular carcinoma. *World J Gastroenterol*. 2018;24(35):3980–3999.
4 Jinato T, Anuntakarun S, Satthawiwat N, Chuaypen N, Tangkijvanich P. Distinct alterations of gut microbiota between viral- and non-viral-related hepatocellular carcinoma. *Appl Microbiol Biotechnol*. 2024;108(1):34.

5 Rosenberg PS, Miranda-Filho A. Cancer incidence trends in successive social generations in the US. *JAMA Netw Open*. 2024;7(6):e2415731.
6 Zhang XF, Liu XM, Wei T, et al. Clinical characteristics and outcome of hepatocellular carcinoma in children and adolescents. *Pediatr Surg Int*. 2013;29(8):763–770.
7 Failli M, Demir S, Del Río-Álvarez Á, et al. Computational drug prediction in hepatoblastoma by integrating pan-cancer transcriptomics with pharmacological response. *Hepatology*. 2024;80(1):55–68.
8 Tanimura M, Matsui I, Abe J, et al. Increased risk of hepatoblastoma among immature children with a lower birth weight. *Cancer Res*. 1998;58:3032–3035.
9 Indolfi G, Easterbrook P, Dusheiko G, et al. Hepatitis B virus infection in children and adolescents. *Lancet Gastroenterol Hepatol*. 2019;4(6):466–476.
10 Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. *Lancet*. 2014;383(9930):1749–1761.
11 *Global burden of disease collaborative network global burden of disease study 2019 (GBD 2019)*. Seattle, United States: Results Institute for Health Metrics and Evaluation (IHME); 2019. Available from: http://ghdx.healthdata.org/gbd-results-tool.
12 Zhai M, Liu Z, Long J, et al. The incidence trends of liver cirrhosis caused by nonalcoholic steatohepatitis via the GBD study 2017. *Sci Rep*. 2021;11(1):5195.
13 Liu Q, He H, Yang J, Feng X, Zhao F, Lyu J. Changes in the global burden of depression from 1990 to 2017: findings from the global burden of disease study. *J Psychiatr Res*. 2020;126:134–140.
14 Kieling C, Buchweitz C, Caye A, et al. Worldwide prevalence and disability from mental disorders across childhood and adolescence: evidence from the global burden of disease study. *JAMA Psychiatr*. 2024;31:e235051.
15 GBD 2021 Other Musculoskeletal Disorders Collaborators. Global, regional, and national burden of other musculoskeletal disorders, 1990-2020, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021. *Lancet Rheumatol*. 2023;5(11):e670–e682.
16 GBD Spinal Cord Injuries Collaborators. Global, regional, and national burden of spinal cord injury, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol*. 2023;22(11):1026–1047.
17 GBD 2021 Neck Pain Collaborators. Global, regional, and national burden of neck pain, 1990-2020, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021. *Lancet Rheumatol*. 2024;6(3):e142–e155.
18 GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020;396(10258):1223–1249.
19 Liu Z, Jiang Y, Yuan H, et al. The trends in incidence of primary liver cancer caused by specific etiologies: results from the Global Burden of Disease Study 2016 and implications for liver cancer prevention. *J Hepatol*. 2019;70(4):674–683.
20 Goodman MT, Gurney JG, Smith MA, et al. *Cancer incidence and survival among children and adolescents: United States SEER Program 1975-1995*. Bethesda, Maryland, USA: National Cancer Institute, SEER Program; 1999:65–72.
21 Chen JC, Chen CC, Chen WJ, Lai HS, Hung WT, Lee PH. Hepatocellular carcinoma in children: clinical review and comparison with adult cases. *J Pediatr Surg*. 1998;33(9):1350–1354.
22 Hung GY, Lin LY, Yu TY, Lee CY, Yen HJ, Horng JL. Hepatoblastoma incidence in Taiwan: a population-based study. *J Chin Med Assoc*. 2018;81(6):541–547.
23 Feng J, Polychronidis G, Heger U, Frongia G, Mehrabi A, Hoffmann K. Incidence trends and survival prediction of hepatoblastoma in children: a population-based study. *Cancer Commun*. 2019;39(1):62.
24 Youlden DR, Baade PD, Green AC, Valery PC, Moore AS, Aitken JF. The incidence of childhood cancer in Australia, 1983-2015, and projections to 2035. *Med J Aust*. 2020;212(3):113–120.
25 Espinoza AF, Patel RH, Patel KR, et al. A novel treatment strategy utilizing panobinostat for high-risk and treatment-refractory hepatoblastoma. *J Hepatol*. 2024;80(4):610–621.
26 Herzog CE, Andrassy RJ, Eftekhari F. Childhood cancers: hepatoblastoma. *Oncologist*. 2000;5(6):445–453.
27 Carrillo-Reixach J, Torrens L, Simon-Coma M, et al. Epigenetic footprint enables molecular risk stratification of hepatoblastoma with clinical implications. *J Hepatol*. 2020;73(2):328–341.
28 Kao JH. Hepatitis B vaccination and prevention of hepatocellular carcinoma. *Best Pract Res Clin Gastroenterol*. 2015;29(6):907–917.
29 Polaris Observatory Collaborators. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. *Lancet Gastroenterol Hepatol*. 2018;3(6):383–403.
30 Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. *Lancet*. 2015;386(10003):1546–1555.
31 Indolfi G, Easterbrook P, Dusheiko G, et al. Hepatitis C virus infection in children and adolescents. *Lancet Gastroenterol Hepatol*. 2019;4(6):477–487.
32 Anderson EL, Howe LD, Jones HE, et al. The prevalence of non-alcoholic fatty liver disease in children and adolescents: a systematic review and meta-analysis. *PLoS One*. 2015;10:e0140908.
33 Nobili V, Alisi A, Valenti L, Miele L, Feldstein AE, Alkhouri N. NAFLD in children: new genes, new diagnostic modalities and new drugs. *Nat Rev Gastroenterol Hepatol*. 2019;16(9):517–530.
34 Lang T, Rayner G. Ecological public health: the 21st century's big idea? An essay by Tim Lang and Geof Rayner. *BMJ*. 2012;345:e5466.
35 Liu S, Veugelers PJ, Liu C, Ohinmaa A. The cost effectiveness of taxation of sugary foods and beverages: a systematic review of economic evaluations. *Appl Health Econ Health Policy*. 2022;20(2):185–198.
36 Sallis JF, Cerin E, Conway TL, et al. Physical activity in relation to urban environments in 14 cities worldwide: a cross-sectional study. *Lancet*. 2016;387(10034):2207–2217.
37 Potvin Kent M, Pauzé E, Bagnato M, et al. Food and beverage advertising expenditures in Canada in 2016 and 2019 across media. *BMC Publ Health*. 2022;22(1):1458.