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ORIGINAL ARTICLE

Global and China Data on the Burden of Liver Cancer Due to Hepatitis B from 1990 to 2021: A Systematic Analysis from the Global Burden of Disease Study 2021

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Abstract

Background: Hepatocellular carcinoma (HCC) is one of the most common gastrointestinal tumors. Hepatitis B virus (HBV) is a major risk factor for hepatocellular carcinoma, and the burden of disease of hepatocellular carcinoma caused by HBV(LCHB) has changed significantly over the past decades. Therefore, the present study analyzed the latest data on LCHB from 1990 to 2021 to identify patterns of HCC incidence, prevalence, and mortality as well as change trends at the age, sex, and socio-demographic index (SDI) levels, and to predict the changing trends of the disease from 2022 to 2050.

Methods: First, the number of incidence, prevalence, deaths, and disability-adjusted life years (DALYs) and the corresponding age-standardized rates (ASRs) were assessed globally and in China in 2021 by different strata to describe the trends from 1990 to 2021. Temporal trends of disease burden from 1990 - 2021 were analyzed by linear regression models. Cluster analysis was used to assess the changing patterns of disease burden associated with the Global Burden of Disease Study (GBD) regions. Finally, ARIMA modeling was used to predict the burden of disease for the next 30 years. Furthermore, we performed frontier and correlation analysis as well as risk factors of the LCHB.

Results: In 2021, the global prevalence of LCHB was 206,366 and the number of deaths was 181,194, representing an increase in prevalence and deaths of 188% and 170%, respectively, compared with 1990. It is noteworthy that the corresponding ASRs of incidence, deaths and DALYs showed an overall decreasing trend, but the ASRs of prevalent showed an increasing trend. Compared to other age groups, the largest increases in ASRs of incidence (estimate annual percentage change (EAPC): 2.94 (2.73-3.15)), mortality (EAPC: 2.78 (2.56-3)) and DALYs (EAPC: 2.72 (2.49-2.95)) were observed in the >95 years age group. Men were at high risk and had a much higher burden of disease than women. Middle SDI regions had the highest disease burden, and age-standardised prevalence rates tended to increase in medium-high and high SDI regions. The disease burden of LCHB varied considerably between GBD regions and countries, with Asia having the highest disease burden of LCHB and Oceania having the lowest. In terms of ASR, East Asia ranked first and southern Latin America ranked last. The pattern of disease change in China is largely consistent with the global pattern of change, with age-standardised prevalence rates, mortality rates and rates of DALYs steadily declining in both men and women, despite the fact that the burden is currently higher in men. In addition, projections show that the number of incidence cases, prevalence cases, deaths, and DALYs cases in both men and women will continue to increase globally and in China from 2022 to 2050, with corresponding stabilisation of ASRs. Frontier analyses suggest that countries or regions with lower SDIs have less potential for burden improvement. Analyses of other risk factors for HCC suggest that smoking remains a major influence on HCC deaths globally, in China, and in Cambodia, albeit with a downward trend in its share. In contrast, the impact of high body mass index(BMI) on HCC has gradually increased.

Conclusion: LCHB remains an important public health problem globally, and although control of anti-HBV infection has led to a decrease in ASRs, we found that the number of cases of incidence, prevalence, deaths, and cases of DALYs are still increasing, and are expected to continue to do so. In addition, unfavorable trends in countries with high SDI and in the elderly suggest that existing prevention strategies may not apply to the changed forms of the disease burden and that more targeted and specific preventive and curative measures for different populations are warranted in some countries to prevent the increase in LCHB.

Keyword: Liver cancer-related HBV, GBD, Global and China

Introduction

Primary liver cancer poses a significant global public health challenge, ranking as the third leading cause of cancer-related deaths in 2022, following lung and colorectal cancers. With approximately 865,000 new cases and 758,000 deaths, it has the fifth-highest incidence rate worldwide. The disease's incidence and mortality rates vary by gender and region specificities, with rates in men being two to three times higher than in women. It is more prevalent in regions with lower economic development, such as East Asia (e.g., Mongolia), Southeast Asia (e.g., Cambodia, Laos, Thailand, and Vietnam), and parts of Africa [1]. China, with its large population, has the highest number of new liver cancer cases and deaths globally, recording 370,000 new cases and 320,000 deaths, which represent the second-highest incidence and fourth-highest mortality rates in the country [1, 2].

HCC is the main pathologic type of primary liver cancer, accounting for about 75-85% of cases. The primary risk factor for HCC is chronic HBV infection, followed by hepatitis C virus (HCV) infection, alcohol consumption, tobacco use, and metabolic factors such as obesity [1, 3]. Globally, around 33% of HCC cases are attributable to HBV infection [4], with rates rising to 60% in Asia and Africa [5].

Recent advancements, including the widespread use of HBV vaccines and direct-acting antiviral drugs, have begun to shift the global landscape of liver cancer causes [3]. The World Health Organization's global hepatitis strategy aims to reduce new hepatitis infections by 90% and deaths by 65% by 2030 [1], which is expected to impact HBV seroprevalence and HCC incidence. However, detailed trends in HCC based on specific etiologies, regional variations, and sociodemographic factors remain underreported. Therefore, there is an urgent need to understand disease patterns and temporal trends in liver cancer to facilitate the development of precisely targeted prevention strategies.

In this study, we utilized data from the GBD 2021 database to analyze the global and Chinese burden of hepatocellular carcinoma caused by HBV (LCHB) from 1990 to 2021. We examined temporal and spatial patterns of changes and trends over this period and projected the disease burden through 2050. Our findings aim to extend existing research and inform the development of targeted liver cancer prevention strategies, ultimately helping to mitigate the global impact of this severe disease.

2. Materials and methods

2.1.1 Overview

GBD Source

Utilizing the latest epidemiological data and advanced standardized methodologies, the 2021 Global Burden of Disease (GBD) study conducts a comprehensive evaluation of the impact caused by 371 different health conditions, injuries, and impairments, alongside 88 contributing factors, spanning 204 countries and regions. The findings of this study are available through the Global Health Data Exchange query tool (http://ghdx.healthdata.org/gbd-results-tool). The database allows for sorting by various categories, including region, sex, and country, and it segments the globe into 27 distinct geographic sectors. To track the prevalence and death rates of LCHB, the study employs age-standardized rates (ASRs) and estimated annual percentage changes (EAPC). The ASRs is pivotal for highlighting changes in disease prevalence within different communities supporting the development of focused preventive measures for LCHB. EAPC provides a summary of ASRs evolution across demographics over designated periods. The Socio-Demographic Index (SDI) serves as an integrated metric for assessing the socio-economic, demographic, and developmental conditions across countries and regions, incorporating elements like per capita GDP, educational levels, and fertility rates. The SDI scale runs from 0 to 1, where higher values denote better socio-economic conditions and lower values indicate lesser development. The analysis categorizes 204 nations and territories into five SDI groups: low, low-middle, middle, high-middle, and high SDI quintiles. This classification aids in the understanding of developmental impacts on health across different areas. The GBD initiative utilizes the DisMod-MR 2.1 software, a Bayesian meta-regression tool, for estimating disease incidence with a methodical cascade process. Before analysis, adjustments are made to ensure data accuracy by disaggregating non-specific age and sex data and employing a Meta-Regression-Bayesian, Regularized, Trimmed (MR-BRT) approach for consistent comparison across different study setups and definitions. Comprehensive details about these adjustments and specific disease corrections can be found in the GBD 2019 capstone report. We conducted a deeper investigation into the effects of secondary and tertiary risk factors, focusing on mortality and disability-adjusted life years (DALYs) associated with Level 2 risks, including alcohol and drug consumption, as well as Level 4 risks, such as high body mass index(BMI). These risk factors were selected in alignment with the guidelines set forth by the World Cancer Research Fund, which underscores significant links between specific risks and health outcomes and uses a comparative risk assessment model. For in-depth methodologies applied to each risk factor, one can refer to the 2021 GBD risk factors capstone report. Additionally, the study incorporates all relevant ICD-9 and ICD-10 codes for primary liver cancer (155, 155.963, and C22.0-9).

2.1.2 Statistical analysis

First, we report the incidence, prevalence, deaths, DALYs, and ASRs of HCC caused by HBV infection for 2021, both globally and in China. Data is presented across various subgroups, including age, sex, SDI, region, and country. By examining ASR trends, we discern patterns of disease change within populations, evaluate the effectiveness of current prevention strategies, and develop more targeted interventions based on these trends.

Second, we analyzed global and Chinese disease burden trends from 1990 to 2021, using a linear regression model to EAPC values. EAPC serves as a summary measure of the trend in ASR over time. An ASR is considered to be increasing if both the EAPC estimate and the lower limit of its 95% confidence interval (CI) are greater than zero; conversely, it is considered to be decreasing if both the EAPC estimate and the upper limit of its 95% CI are less than zero. If the EAPC estimate and its CI boundaries do not consistently indicate an upward or downward trend, the ASR is deemed stable. Additionally, hierarchical cluster analysis was conducted globally to assess the changing patterns of disease burden across the 45 GBD regions, categorizing them into four groups: significantly increasing, slightly increasing, stable or slightly decreasing, and significantly decreasing.

Finally, in our study, we employed frontier analysis as a rigorous methodology to establish benchmarks for assessing the burden of LCHB across diverse countries and territories. This approach facilitates a comparative evaluation, benchmarking each entity against the most performant counterparts, thereby pinpointing leader countries and establishing benchmarks that can guide and motivate other countries. Specifically, we calculated the 'effective difference' metric for each country and territory, which quantifies the discrepancy between the current incidence of liver cancer attributable to LCHB and its potential optimal level, adjusted for Sociodemographic Index (SDI). This adjustment ensures that comparisons are equitable, accounting for variations in socioeconomic and demographic profiles that can significantly influence disease outcomes. In addition, Correlation analysis, a statistical approach to evaluate the linear interdependencies between pairs of variables, was conducted using R's cor.test function to calculate the correlation coefficients among EAPC, ASIR, ASPR, and HDI. The relationships were graphically represented in scatter plots, enhanced with trend lines to visually interpret the data.

To forecast future trends in LCHB prevalence and incidence, we applied the ARIMA

(AutoRegressive Integrated Moving Average) model. This technique requires transforming the time series data to a stationary state through differencing prior to analysis. The model is defined by three main parameters: p (autoregressive order), d (differencing order), and q (moving average order). These parameters were set based on analyses performed with tools like the autocorrelation function (ACF) and the partial autocorrelation function (PACF). Forecasting was conducted using the forecast and tseries packages in R, facilitating both prediction and graphical display of the results. To ensure the reliability of our forecasts, various validation techniques were applied: checking the independence of forecast errors via the Ljung-Box Q-test, confirming the normal distribution of residuals with a mean of zero by the Shapiro-Wilk test, and evaluating the homoscedasticity of residuals through visual inspection and the Breusch-Pagan test. Statistical significance was determined with a P-value threshold of 0.05. Data construction, organization, and analysis were performed using R software (version 4.3.2).

3. Results

3.1 2021 Global Burden of LCHB

In 2021, the global prevalence of LCHB was 206,366 cases [95% uncertainty interval (UI): 169,401-252,050], with 181,194 deaths [95% UI: 148,896-221,685] (**Tables 1-2**).

Table 1: The number of deaths cases and the age-standardized deaths rate attributable to LCHB in 1990 and 2021, and its trends from 1990 to 2021 globally.

Characteristics	Number of deaths cases (95% UI) in 1990	The age-standardized deaths rate/100000 (95% UI) in 1990	Number of deaths cases (95% UI) in 2021	The age-standardized deaths rate/100000 (95% UI) in 2021	EAPC (95% CI)
Global	106,514 (91,940-124291)	2.5 (2.15-2.92)	181,194(148,896-221,685)	2.09 (1.72-2.55)	-0.65 (-0.79--0.51)
Female	20,475 (16,329-25,357)	0.93 (0.74-1.16)	34,689 (27,676-42,913)	0.76 (0.61-0.94)	-0.68 (-0.77--0.6)
Male	86,040 (73,638-100,603)	4.2 (3.59-4.92)	146,506 (118,397-182,374)	3.54 (2.87-4.41)	-0.62 (-0.77--0.48)
10-14 years	371 (318-436)	0.07 (0.06-0.08)	232 (189-289)	0.03 (0.03-0.04)	-2.76 (-3.12--2.39)
15-19 years	544 (459-653)	0.1 (0.09-0.13)	398 (326-486)	0.06 (0.05-0.08)	-1.81 (-2--1.61)
20-24 years	1,059 (899-1,261)	0.22 (0.18-0.26)	766 (657-897)	0.13 (0.11-0.15)	-2.21 (-2.41--2.01)
25-29 years	2,006 (1,685-2,425)	0.45 (0.38-0.55)	1,855 (1,543-2,202)	0.32 (0.26-0.37)	-1.87 (-2.35--1.4)
30-34 years	3,722 (3,171-4,439)	0.97 (0.82-1.15)	4,298 (3,627-5,225)	0.71 (0.6-0.86)	-1.92 (-2.41--1.43)
35-39 years	6,304 (5,327-7,506)	1.79 (1.51-2.13)	6,565 (5,393-8,091)	1.17 (0.96-1.44)	-1.81 (-2.12--1.49)
40-44 years	9,064 (7,525-10,678)	3.16 (2.63-3.73)	9,779 (7,795-11,921)	1.95 (1.56-2.38)	-1.76 (-1.97--1.55)
45-49 years	10,680 (8,932-12,741)	4.6 (3.85-5.49)	15,960 (12,714-19,986)	3.37 (2.69-4.22)	-0.94 (-1.26--0.63)
50-54 years	13,274 (10,989-15,842)	6.24 (5.17-7.45)	22,036 (16,990-28,276)	4.95 (3.82-6.36)	-0.64 (-0.86--0.42)
55-59 years	14,644 (11,878-17,764)	7.91 (6.41-9.59)	24,210 (18,560-31,752)	6.12 (4.69-8.02)	-0.97 (-1.14--0.79)
60-64 years	14,177 (10,945-17,601)	8.83 (6.81-10.96)	22,592 (15,948-30,386)	7.06 (4.98-9.49)	-0.67 (-0.82--0.52)
65-69 years	12,211 (9,454-15,090)	9.88 (7.65-12.21)	24,181 (17,905-30,552)	8.77 (6.49-11.08)	-0.46 (-0.65--0.26)

70-74 years	8,944 (6,685-11,574)	10.56 (7.9-13.67)	18,460 (13,218-23,742)	8.97 (6.42-11.53)	-0.67 (-0.85--0.49)
75-79 years	5,612 (4,301-7,044)	9.12 (6.99-11.44)	13,187 (10,050-16,643)	10 (7.62-12.62)	0.13 (-0.09-0.36)
80-84 years	2,613 (1,915-3,469)	7.39 (5.41-9.81)	9,582 (6,822-12,413)	10.94 (7.79-14.17)	1.78 (1.5-2.06)
85-89 years	1,041 (778-1,386)	6.89 (5.15-9.17)	5,027 (3,721-6,657)	10.99 (8.14-14.56)	1.75 (1.6-1.9)
90-94 years	221 (150-330)	5.16 (3.49-7.69)	1,733 (1,191-2,448)	9.69 (6.66-13.69)	2.14 (1.96-2.32)
95+ years	28 (14-49)	2.73 (1.42-4.81)	336 (183-549)	6.16 (3.36-10.07)	2.78 (2.56-3)
High-middle SDI	29,654 (24,699-35,265)	2.86 (2.39-3.41)	47,895 (37,909-60,440)	2.5 (1.99-3.16)	-0.65 (-0.89--0.41)
High SDI	15,699 (13,141-18,507)	1.5 (1.26-1.77)	22,541 (18,388-27,202)	1.17 (0.97-1.4)	-0.95 (-1.11--0.78)
Low-middle SDI	8,694 (6,805-11,281)	1.27 (0.99-1.64)	18,249 (14,603-23,064)	1.18 (0.95-1.49)	-0.45 (-0.52--0.38)
Low SDI	6,894 (4,538-9,894)	2.79 (1.84-4)	11,352 (8,479-14,986)	1.97 (1.47-2.62)	-1.32 (-1.46--1.19)
Middle SDI	45,528 (38,954-52,953)	3.86 (3.31-4.5)	81,087 (64,898-101,641)	2.92 (2.35-3.64)	-0.81 (-0.93--0.68)

Table 2: The number of DALYs cases and the age-standardized DALYs rate attributable to LCHB in 1990 and 2021, and its trends from 1990 to 2021 globally.

Characteristics	Number of DALYs cases (95% UI) in 1990	The age-standardized DALYs rate /100000 (95% UI) in 1990	Number of DALYs cases (95% UI) in 2021	The age-standardized DALYs rate/100000 (95% UI) in 2021	EAPC (95% CI)
Global	3,748,179 (3,255,634-4,362,511)	84.16 (73.1-97.96)	5,668,199 (4,706,886-6,885,071)	65.36 (54.43-79.35)	-0.94 (-1.09--0.79)
Female	676,140 (551,000-817,561)	29.78 (24.25-36.3)	999,293 (814,569-1,216,039)	22.5 (18.37-27.27)	-1.04 (-1.14--0.94)
Male	3,072,039 (2,626,206-3,564,854)	140.16 (119.77-162.77)	4,668,906 (3,794,780-5,803,284)	110.11 (89.43-136.48)	-0.9 (-1.05--0.74)
10-14 years	28,882 (24,693-33,932)	5.39 (4.61-6.33)	18,032 (14,723-22,485)	2.7 (2.21-3.37)	-2.76 (-3.12--2.4)
15-19 years	39,575 (33,438-47,559)	7.62 (6.44-9.16)	28,937 (23,733-35,350)	4.64 (3.8-5.67)	-1.81 (-2--1.61)
20-24 years	71,974 (61,083-85,615)	14.63 (12.41-17.4)	52,006 (44,618-60,935)	8.71 (7.47-10.2)	-2.21 (-2.41--2.02)
25-29 years	126,589 (106,307-153,073)	28.6 (24.02-34.58)	116,839 (97,245-138,803)	19.86 (16.53-23.59)	-1.87 (-2.35--1.4)
30-34 years	215,464 (183,491-256,908)	55.9 (47.61-66.66)	249,285 (210,350-303,268)	41.24 (34.8-50.17)	-1.91 (-2.4--1.42)
35-39 years	334,530 (282,690-398,457)	94.97 (80.25-113.12)	348,910 (286,731-430,183)	62.21 (51.12-76.7)	-1.8 (-2.12--1.49)
40-44 years	436,331 (362,194-513,776)	152.31 (126.43-179.34)	470,798 (375,414-573,108)	94.11 (75.05-114.56)	-1.77 (-1.97--1.56)
45-49 years	461,271 (386,119-550,406)	198.66 (166.29-237.04)	689,390 (549,331-863,689)	145.59 (116.01-182.4)	-0.94 (-1.26--0.63)

50-54 years	509,745 (422,188-607,747)	239.8 (198.61-285.9)	847,678 (652,523-1,087,413)	190.52 (146.66-244.4)	-0.64 (-0.86--0.41)
55-59 years	494,279 (400,944-599,170)	266.89 (216.49-323.53)	818,757 (627,726-1,074,547)	206.9 (158.63-271.54)	-0.96 (-1.13--0.78)
60-64 years	412,703 (318,849-512,502)	256.96 (198.52-319.1)	657,719 (464,038-884,622)	205.51 (144.99-276.4)	-0.67 (-0.82--0.51)
65-69 years	299,402 (231,798-369,543)	242.22 (187.52-298.96)	593,350 (439,084-749,084)	215.1 (159.18-271.56)	-0.45 (-0.65--0.25)
70-74 years	180598 (135123-233672)	213.32 (159.61-276.01)	373256 (267056-481055)	181.33 (129.74-233.7)	-0.67 (-0.85--0.49)
75-79 years	90,926 (69,648-114,127)	147.71 (113.15-185.41)	213,184 (162,005-269,489)	161.64 (122.84-204.34)	0.12 (-0.1-0.35)
80-84 years	33,212 (24,381-44,072)	93.88 (68.92-124.58)	121,348 (86,371-157,575)	138.55 (98.62-179.91)	1.77 (1.49-2.05)
85-89 years	10,529 (7,858-14,036)	69.68 (52-92.89)	50,774 (37,573-67,419)	111.05 (82.18-147.46)	1.75 (1.6-1.89)
90-94 years	1,939 (1,314-2,884)	45.24 (30.67-67.3)	15,200 (10,446-21,489)	84.97 (58.39-120.12)	2.14 (1.96-2.32)
95+ years	230 (120-404)	22.55 (11.77-39.72)	2,734 (1,495-4,476)	50.17 (27.43-82.13)	2.72 (2.49-2.95)
High-middle SDI	1,055,382 (880,686-1,247,422)	100.12 (83.52-118.58)	1,487,086 (1,177,832-1,882,872)	80.79 (64.35-102.24)	-1.01 (-1.27--0.75)
High SDI	499,137 (424,579-590,146)	49.07 (41.64-57.82)	577,543 (479,217-691,358)	33.5 (28.16-39.8)	-1.43 (-1.6--1.26)
Low-middle SDI	307,387 (241,167-392,407)	40.35 (31.69-51.9)	615,623 (494,362-769,789)	36.97 (29.77-46.5)	-0.51 (-0.6--0.43)
Low SDI	237,066 (157,821-332,320)	84.29 (55.5-120.55)	403,657 (304,906-539,507)	60.42 (45.26-80.28)	-1.28 (-1.41--1.14)
Middle SDI	1,647,718 (1,400,349-1,931,330)	127.53 (108.54-149.01)	2,582,133 (2,080,861-3,255,381)	90.66 (73.31-114.04)	-1.06 (-1.2--0.93)

According to Figure 1A-B, ASRs show an increase and subsequent decrease with age, peaking at 85–89 years for incidents and mortality. However, ASR of prevalence and DALYs remained elevated in the 65–69 age group. The number of cases for incidence, prevalence, deaths, and DALYs follows a similar age-related pattern (**Tables 1-2**).

Globally, men experienced higher ASRs for incidence, prevalence, mortality, and DALYs from LCHB compared to women. In 2021, the number of prevalent cases and deaths among men were 168,980 and 146,506, respectively, which was 4.87 and 4.22 times higher than those among women. The corresponding ASRs were 4.87 times and 4.70 times higher for men **(Figure 1B, Table 1-4).**

Table 3: The number of incidence cases and the age-standardized incidence rate attributable to LCHB in 1990 and 2021, and its trends from 1990 to 2021 globally.

Characteristics	Number of incidence cases (95% UI) in 1990	The age-standardized incidence rate/100000 (95% UI) in 1990	Number of incidence cases (95% UI) in 2021	The age-standardized incidence rate/100000 (95% UI) in 2021	EAPC (95% CI)
Global	109,479 (94,820-127,366)	2.55 (2.2-2.97)	206,366 (169,401-	2.37 (1.95-2.89)	-0.27 (-0.39--0.15)

			252,050)		
Female	20,590 (16,481-25,416)	0.93 (0.75-1.15)	37,386 (30,021-46,242)	0.83 (0.67-1.02)	-0.45 (-0.53--0.38)
Male	88,888 (76,231-103,337)	4.27 (3.66-4.97)	168,980 (135, 836-210, 076)	4.04 (3.26-5.01)	-0.21 (-0.34--0.08)
10-14 years	333 (280-398)	0.06 (0.05-0.07)	206 (162-262)	0.03 (0.02-0.04)	-2.82 (-3.19--2.46)
15-19 years	560 (473-672)	0.11 (0.09-0.13)	436 (361-532)	0.07 (0.06-0.09)	-1.6 (-1.78--1.42)
20-24 years	1,049 (893-1,246)	0.21 (0.18-0.25)	824 (712-966)	0.14 (0.12-0.16)	-2 (-2.19--1.81)
25-29 years	2,175 (1,823-2,627)	0.49 (0.41-0.59)	2,240 (1,868-2,657)	0.38 (0.32-0.45)	-1.54 (-1.99--1.09)
30-34 years	4,096 (3,498-4,891)	1.06 (0.91-1.27)	5,409 (4,549-6,580)	0.89 (0.75-1.09)	-1.5 (-1.93--1.06)
35-39 years	7,324 (6,178-8,679)	2.08 (1.75-2.46)	8,730 (7,178-10,765)	1.56 (1.28-1.92)	-1.41 (-1.7--1.13)
40-44 years	10,125 (8,445-11,931)	3.53 (2.95-4.16)	12,704 (10,108-15,424)	2.54 (2.02-3.08)	-1.22 (-1.38--1.06)
45-49 years	11,661 (9,775-13,843)	5.02 (4.21-5.96)	20,538 (16,279-25,782)	4.34 (3.44-5.44)	-0.33 (-0.63--0.02)
50-54 years	14,301 (11,841-17,046)	6.73 (5.57-8.02)	27,870 (21,552-35,833)	6.26 (4.84-8.05)	-0.03 (-0.22-0.16)
55-59 years	15,270 (12,424-18,502)	8.25 (6.71-9.99)	28,525 (21,919-37,455)	7.21 (5.54-9.46)	-0.57 (-0.71--0.43)
60-64 years	14,399 (11,125-17,854)	8.97 (6.93-11.12)	25,793 (18,170-34,348)	8.06 (5.68-10.73)	-0.24 (-0.41--0.08)
65-69 years	11,890 (9,222-14,671)	9.62 (7.46-11.87)	26,187 (19,396-33,025)	9.49 (7.03-11.97)	-0.08 (-0.25-0.09)
70-74 years	8,284 (6,192-10,674)	9.78 (7.31-12.61)	19,150 (13,787-24,720)	9.3 (6.7-12.01)	-0.31 (-0.47--0.14)
75-79 years	4,899 (3,767-6,136)	7.96 (6.12-9.97)	12,815 (9,750-16,181)	9.72 (7.39-12.27)	0.48 (0.27-0.69)
80-84 years	2,128 (1,545-2,821)	6.02 (4.37-7.97)	8,678 (6,207-11,188)	9.91 (7.09-12.77)	2.15 (1.87-2.44)
85-89 years	816 (608-1,084)	5.4 (4.02-7.18)	4,798 (3,584-6,326)	10.49 (7.84-13.84)	2.37 (2.24-2.49)
90-94 years	152 (103-227)	3.54 (2.4-5.29)	1,248 (855-1,756)	6.97 (4.78-9.82)	2.32 (2.14-2.51)
95+ years	17 (9-30)	1.71 (0.89-2.98)	216 (116-352)	3.96 (2.14-6.46)	2.94 (2.73-3.15)
High-middle SDI	30,404 (25,390-36,206)	2.92 (2.44-3.48)	55,363 (43,590-70,055)	2.92 (2.31-3.69)	-0.17 (-0.39-0.04)
High SDI	17,146 (14,407-20,205)	1.65 (1.39-1.94)	28,989 (23,732-34,830)	1.56 (1.29-1.85)	-0.32 (-0.53--0.12)
Low-middle SDI	8,663 (6,781-11,211)	1.24 (0.96-1.6)	18,220 (14,529-22,911)	1.15 (0.93-1.45)	-0.42 (-0.49--0.36)
Low SDI	6,812 (4,488-9,757)	2.68 (1.75-3.83)	11,303 (8,431-14,885)	1.9 (1.42-2.52)	-1.32 (-1.45--1.19)
Middle SDI	46,407 (39,575-54,127)	3.86 (3.3-4.49)	92,419 (73,621-117,265)	3.29 (2.63-4.15)	-0.39 (-0.52--0.26)

Table 4: The number of prevalence cases and the age-standardized prevalence rate attributable to LCHB in 1990 and 2021, and its trends from 1990 to 2021 globally.

Characteristics	Number of prevalence cases (95% UI) in 1990	The age-standardized prevalence rate/ 100 0 00 (95% UI) in 1990	Number of prevalence cases (95% UI) in 2021	The age-standardized prevalence rate/ 100 000 (95% UI) in 2021	EAPC (95% CI)
Global	138,790 (121,366-160,866)	3.14 (2.74-3.64)	288,106 (237,812-349,750)	3.32 (2.74-4.02)	0.14 (0.02-0.27)
Female	25,335 (20,628-30, 801)	1.12 (0.91-1.37)	49,711 (40,22 5-60,983)	1.11 (0.9-1.36)	-0.1 (-0.19--0.02)
Male	113,455 (97,646-131,135)	5.24 (4.51-6.06)	238,395 (193,233-296,324)	5.65 (4.59-7.01)	0.23 (0.09-0.36)
10-14 years	622 (523-743)	0.12 (0.1-0.14)	403 (321-515)	0.06 (0.05-0.08)	-2.66 (-3.02--2. 3)
15-19 years	943 (797-1,132)	0.18 (0.15-0.22)	766 (636-934)	0.12 (0.1-0.15)	-1.45 (-1.63--1.27)
20-24 years	1,673 (1,426-1,984)	0.34 (0.29-0.4)	1,378 (1,193-1,613)	0.23 (0.2-0.27)	-1.83 (-2.02--1.65)
25-29 years	5,135 (4,307-6,205)	1.16 (0.97-1.4)	5,544 (4,636-6,555)	0.94 (0.79-1.11)	-1.37 (-1.81--0.92)
30-34 years	8,640 (7,381-10,305)	2.24 (1.92-2.67)	11,984 (10,07 7-14,543)	1.98 (1.67-2.41)	-1.32 (-1.76--0.89)
35-39 years	12,385 (10,460-14,655)	3.52 (2.97-4.16)	15,680 (12,86 1-19,283)	2.8 (2.29-3.44)	-1.2 (-1.49--0.92)
40-44 years	13,241 (11,087-15,562)	4.62 (3.87-5.43)	19,120 (15,33 8-23,319)	3.82 (3.07-4.66)	-0.71 (-0.87--0.56)
45-49 years	15,306 (12,807-18,135)	6.59 (5.52-7.81)	31,351 (24,74 8-39,09 1)	6.62 (5.23-8.26)	0.21 (-0.07-0.48)
50-54 years	18,448 (15,274-21,981)	8.68 (7.19-10.34)	41,891 (32,5 42-53,827)	9.42 (7.31-12.1)	0.53 (0.33-0.72)
55-59 years	19,046 (15,591-23,083)	10.28 (8.42-12.46)	40,886 (31,4 32-54,180)	10.33 (7.94-13.69)	-0.05 (-0.22-0.11)
60-64 years	16,478 (12,733-20,423)	10.26 (7.93-12.72)	35,070 (2,47 31-46,224)	10.96 (7.73-14.44)	0.37 (0.22-0.53)
65-69 years	12,685 (9,866-15,634)	10.26 (7.98-12.65)	33,176 (24,50 5-41,765)	12.03 (8.88-15.14)	0.53 (0.36-0.7)
70-74 years	7,719 (5,772-9,928)	9.12 (6.82-11.73)	21,918 (15,70 1-28,486)	10.65 (7.63-13.84)	0.43 (0.24-0.62)
75-79 years	4,188(3,216-5,245)	6.8 (5.22-8.52)	14,043 (10,66 4-17,875)	10.65 (8.09-13.55)	1.36 (1.13-1.59)
80-84 years	1,631 (1,191-2,155)	4.61 (3.37-6.09)	9,090 (6,358-11,840)	10.38 (7.26-13.52)	3.22 (2.93-3.51)
85-89 years	552 (414-731)	3.65 (2.74-4.84)	4,842 (3,571-6,432)	10.59 (7.81-14.07)	3.66 (3.53-3.8)
90-94 years	89 (60-133)	2.08 (1.41-3.11)	852 (584-1,20 1)	4.77 (3.27-6.72)	2.82 (2.66-2.98)
95+ years	9 (5-15)	0.86 (0.45-1.51)	111 (60-181)	2.04 (1.1-3.31)	2.99 (2.79-3.2)
SDI region					
High-middle SDI	38,328 (32,064-45,238)	3.63 (3.04-4.3)	76,540 (60,5 28-96,594)	4.12 (3.27-5.18)	0.22 (0-0.43)
High SDI	23,253 (19,785-27,227)	2.26 (1.95-2.65)	50,881 (41,695 -60,88 0)	2.86 (2.39-3.37)	0.73 (0.39-1.07)
Low-middle SDI	10,572 (8,259-13,568)	1.42 (1.11-1.83)	22,172 (17,7 83-27,797)	1.35 (1.08-1.7)	-0.37 (-0.4 4- -0.3)
Low SDI	8,094 (5,346-11,435)	2.95 (1.94-4.23)	13,952 (10,5 32-18,465)	2.15 (1.6-2.84)	-1.23 (-1.3 6--1.11)
Middle SDI	58,489 (49,836-68,570)	4.6 (3.93-5.36)	124,473 (99,281-157,937)	4.38 (3.5-5.54)	-0.04 (-0.2-0. 12)

Men had 4,668,906 DALYs, 4.67 times higher than the 999,293 DALYs for women, with an ASR of 4.89 times greater.

By SDI, the middle SDI region in 2021 reported the highest number of deaths (81,087 cases) and DALYs (2,582,133 cases), along with the highest ASRs of incidence (3.29; 95% UI: 2.63-4.15), prevalence (4.38; 95% UI: 3.5-5.54), mortality (2.92; 95% UI: 2.35- 3.64), and ASR of DALY (90.66; 95% UI: 73.31-114.04) in the middle SDI region (**Figure 1C**).

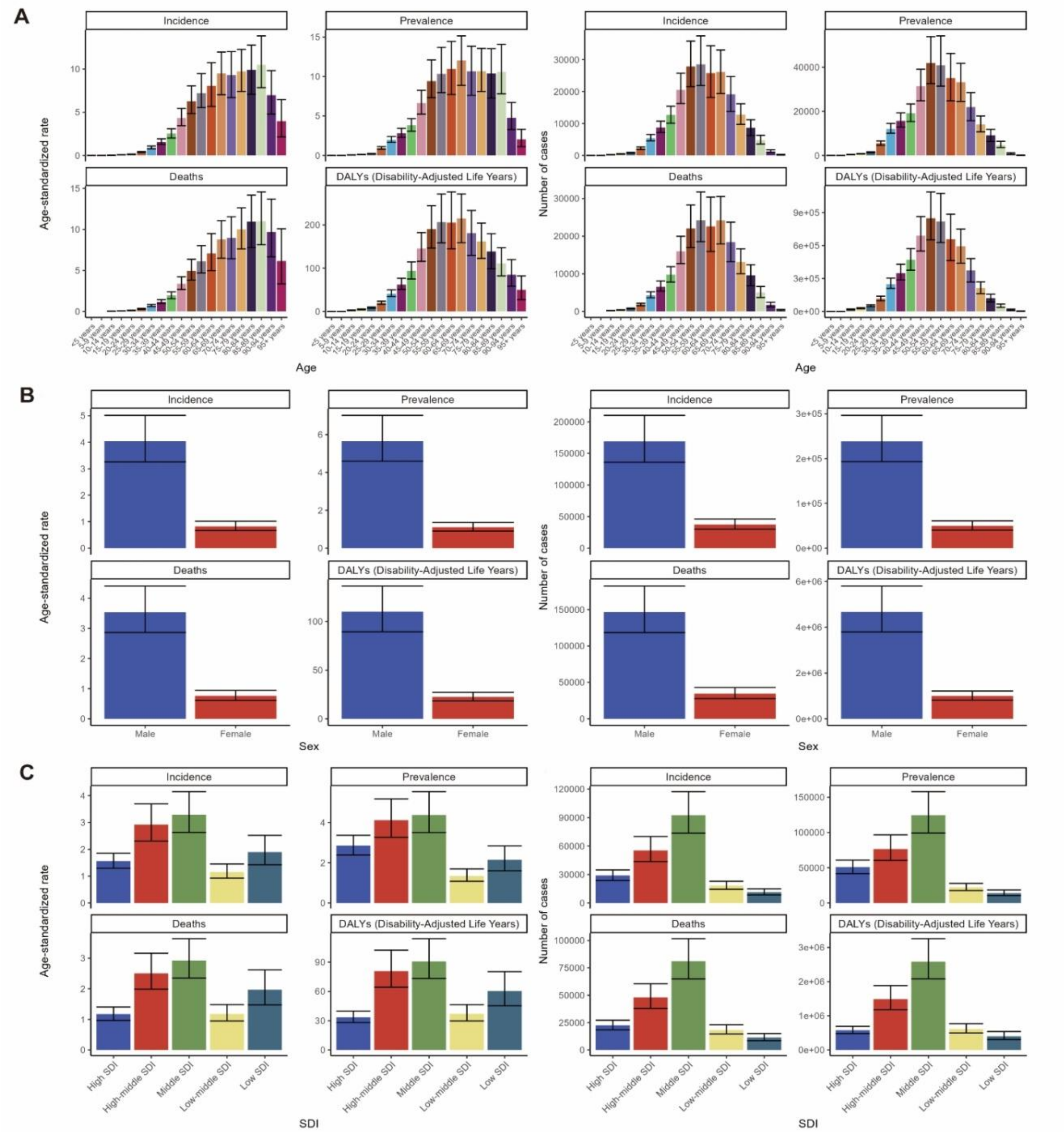

Figure 1: The number of LCHB-related deaths, DALYs, incidence, and prevalence globally by age group (A), sex (B), SDI region (C) and the corresponding age-standardized rates in 2021. Abbreviations: DALYs, disability-adjusted-life-years. LCHB, Liver cancer related to Hepatitis B virus (HBV)

Among the 54 GBD regions, Asia had the highest incidence (173, 173 cases; 95% UI: 140, 487-213, 579), deaths (149, 743 cases; 95% UI: 121, 986-184, 486), prevalence (243, 634 cases; 95% UI: 198, 370-299, 526), and DALYs (4, 669, 732 cases; 95% UI: 3, 826, 961-5, 773, 574) of LCHB, followed by East Asia and the Pacific, while Oceania had the lowest figures. In terms of ASRs, East Asia ranked first in ASRs of prevalence (5.7; 95% UI: 4.49-7.29), mortality (4.81; 95% UI:

3.78-6.13), and DALYs (155.12; 95% UI: 122.1-199.6), whereas Southern Latin America had the lowest rates (ASRs of incidence: 0.32; 95% UI: 0.23-0.46; prevalence: 0.39,95% UI: 0.28-0.53; mortality: 0.32; 95% UI: 0.22-0.46; DALYs: 9.11; 95% UI: 6.53-12.54) **(Figure 2A)**.

At the country level, there was significant variation in disease burden due to HBV infection. In 2021, Mongolia had the highest ASRs of incidence (16.61; 95% UI: 10.77-24.42) and mortality (17.18; 95% UI: 11.03-25.21) per 100,000 populations. South Korea had the highest ASRs of prevalence (21.97; 95% UI: 17.5-27.73), and the Gambia had the highest ASRs of DALYs (531.32; 95% UI: 327-792). In absolute terms, China had the highest number of morbidity (118,665 cases; 95% UI: 92,280-153,556), prevalence (165,217 cases; 95% UI: 129,037-215,080), mortality (12,249 cases; 95% UI: 10 294-14, 737), and DALYs (3,148,553 cases; 95% UI: 2,442,865-4,109,014) cases. San Marino, Tuvalu, Niue, Tokelau, and Nauru had the lowest number of cases, prevalence, and deaths, nearing zero

(**Figure 2B**).

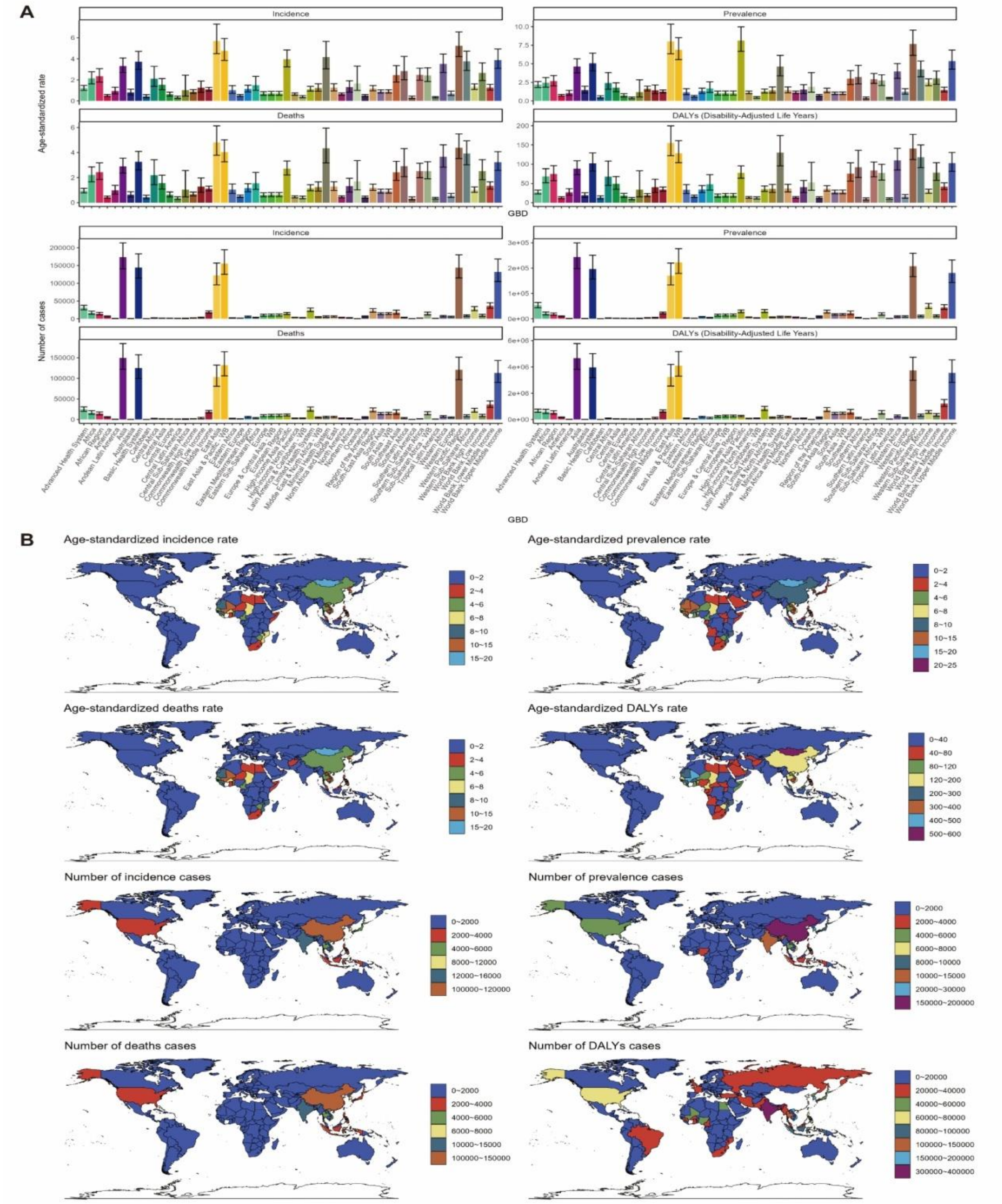

Figure 2: The number of LCHB-related deaths, DALYs, incidence, and prevalence globally by GBD region (A), country (B) and the corresponding age-standardized rates in 2021.

3.2 Trends in Global LCHB Burden 1990 – 2021

Between 1990 and 2021, the global incidence of LCHB rose by 88.5%, from 109,479 cases in 1990 to 206,366 cases in 2021. The number of deaths increased by 70.1%, from 106,514 to 181,194, while DALYs grew by 51.2%. Overall, both the number of cases of incidence, prevalence, deaths and DALYs displayed a general upward trend.

In contrast, ASRs for incidence, deaths, and DALYs demonstrated an overall decreasing trend: the EAPC for incidence was -0.27 (95% CI: -0.39 to -0.15), for deaths was -0.65 (95% CI: -0.79 to -0.51), and for DALYs was -0.94 (95% CI: -1.09 to -0.79). Conversely, the number of prevalent cases increased from 138,790 to 288,106, with an ASRs showing an upward trend (EAPC: 0.14; 95% CI: 0.02-0.27) (**Figure 3A**).

From 1990 to 2021, ASRs of incidence, prevalence, and mortality generally increased across most age groups. The most notable rises in annual percentage change were observed in the over-95 years age group, with standardized morbidity increasing at an EAPC of 2.94 (95% CI: 2.73 to 3.15) and standardized mortality rising at an EAPC of 2.78 (95% CI: 2.56 to 3.00). The 85-89 age group experienced the most significant increase in age-standardized prevalence over the decades, with an EAPC of 3.66 (95% CI: 3.53 to 3.80). In contrast, age-standardized DALYs generally showed a downward trend across most age groups, though the over-95 years age group was an exception, where age-standardized DALYs continued to rise at an EAPC of 2.72 (95% CI: 2.49 to 2.95) (**Figure 3B**).

Since 1990, the ASRs of prevalence in males showed an increasing trend (EAPC: 3.66; 95% CI: 3.53 to 3.80), while ASRs of incidence, mortality, and DALY rates were decreased for both genders, with a more pronounced decline in females. From 1990 to 2021, the number of cases of LCHB increased for both genders (**Figure 3C**).

At the level of SDI regions, ASRs of incidence, prevalence, mortality, and DALY exhibited a decreasing trend across all SDI regions. However, in medium- and high-SDI regions, the annual percentage change in the ASR of prevalence showed an increasing trend (**Figure 3D**).

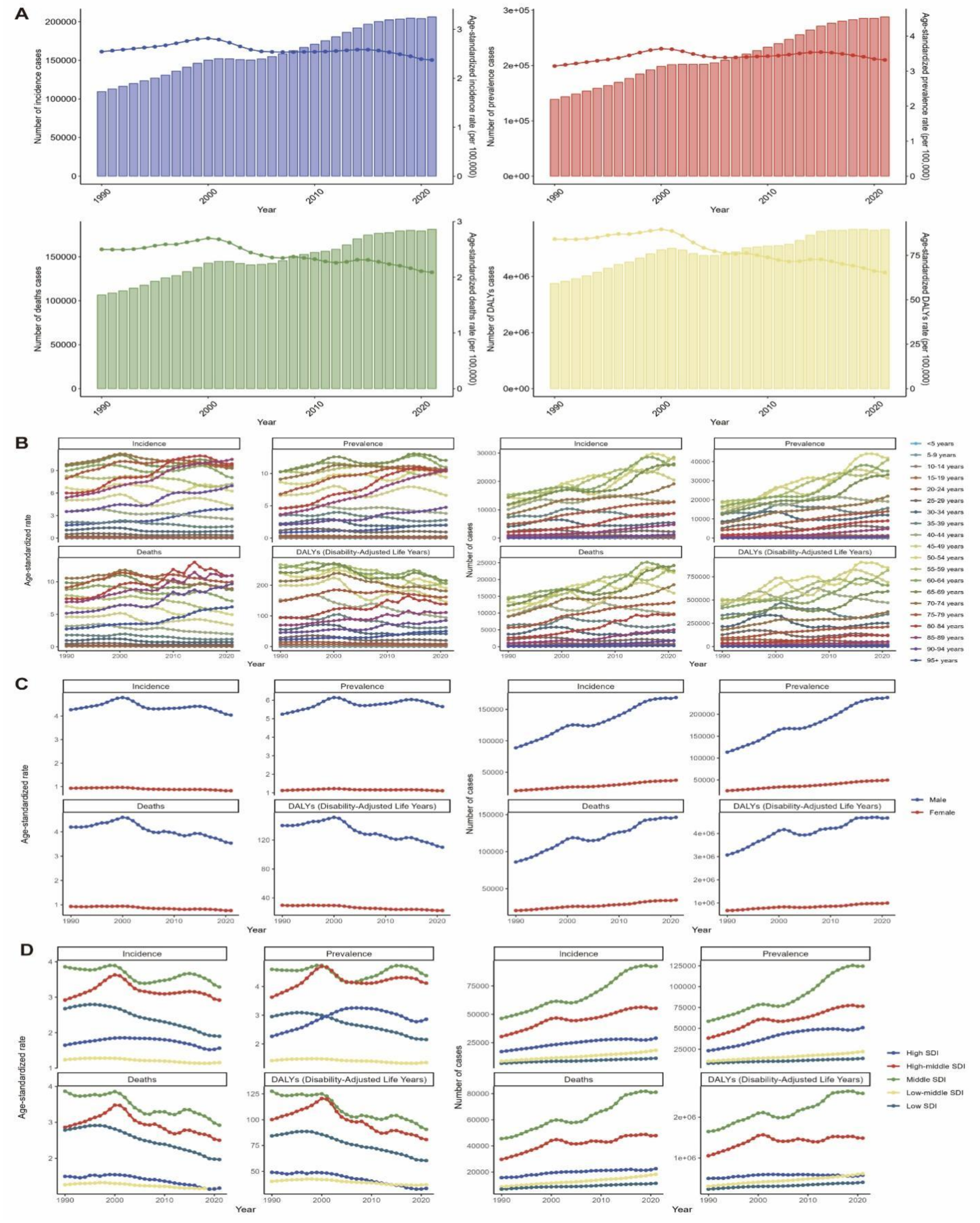

Figure 3: Temporal trend for LCHB-related disease burden from 1990 to 2021.
(A-D) Time trends in the global burden of disease associated with LCHB, 1990-2021 (A), and by age group (B), gender (C), and SDI region (D).

The burden of LCHB exhibited a significant regional and national variation globally. Australia experienced the most dramatic increases in both incidence and prevalence cases, with the incidence rate rising by 439.0% from 59 cases in 1990 to 318 cases in 2021 and prevalence increasing by 571.8% from 78 to 524 cases. Regarding deaths and DALYs, the United Arab Emirates saw the largest increases, with deaths rising by 917.7% and DALYs by 902.8%, followed by Qatar with increases of 760.0% in deaths and 699.5% in DALYs. Conversely, the largest decreases were observed in Mauritius and Bulgaria, where deaths decreased by 61.5% and 59.9%, and DALYs decreased by 65.9% and 62.3%, respectively (**Figure 4A**).

Between 1990 and 2021, the UK experienced the most significant increases in ASRs for LCHB incidence, prevalence, deaths, and DALYs, with an EAPC of 4.66 (95% CI: 4.39 to 4.93) for incidence, 5.67 (95% CI: 5.33 to 6.01) for prevalence, 4.01 (95% CI: 3.75-4.27) for deaths, and 3.90 (95% CI: 3.64 to 4.17) for DALYs. Conversely, Zambia recorded the largest decreases in incidence and prevalence cases, with EAPCs of -4.44 (95% CI: -5.20 to -3.67) and -4.39 (95% CI: -5.14 to -3.64), respectively. The most substantial decreases in deaths and DALYs occurred in Kuwait, with EAPCs of -4.45 (95% CI: -5.44 to -3.45) for deaths and -4.85 (95% CI: -5.82 to -3.86) for DALYs (**Figure 4B**).

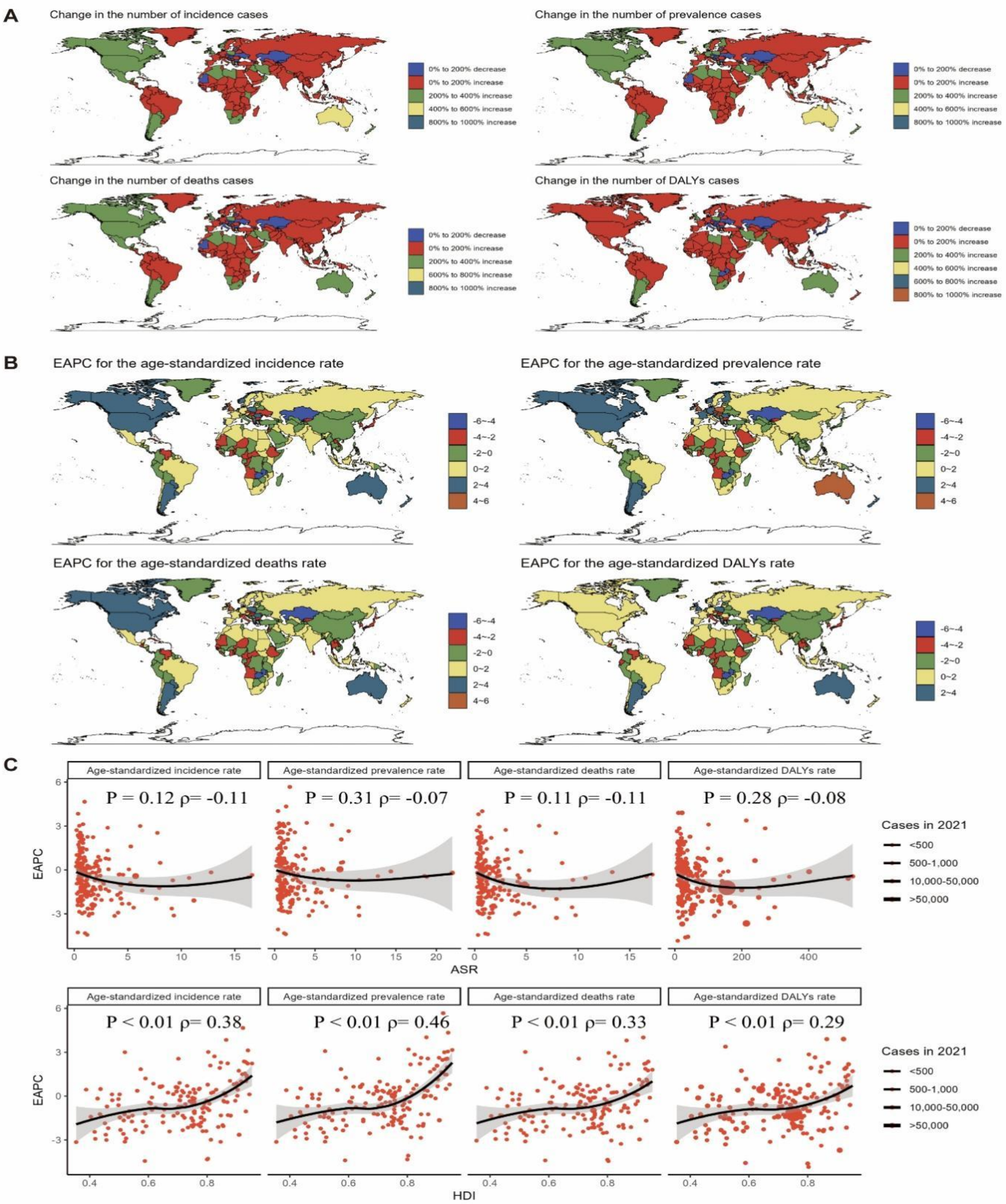

Figure 4: Changes in different countries and regions (A) and EAPC(B) for ASIR, ASPR, ASDR, ASR of DALYs. The association between EAPCs and LCHB-related ASRs in 1990 and HDIs in 2021(C). The circles represent countries that were available on HDI data. The size of the circle is increased with the cases of LCHB. The ρ indices and p values presented were derived from Spearman correlation analysis. (P value > 0.05 was statistically significant)
Abbreviations: ASR, age-standardized rate; HDI, human development index.

Hierarchical cluster analysis identified regions with similar disease burden changes. The top four regions with significant increases in incidence, prevalence, mortality, and DALYs were the World Bank Low Income, African Region, Sub-Saharan Africa - WB, and Central Asia. In contrast, the regions with the most significant decreases were Southern Sub-Saharan Africa, Commonwealth Middle Income, Latin America and Caribbean - WB, and the Eastern Mediterranean Region (**Figure 5**).

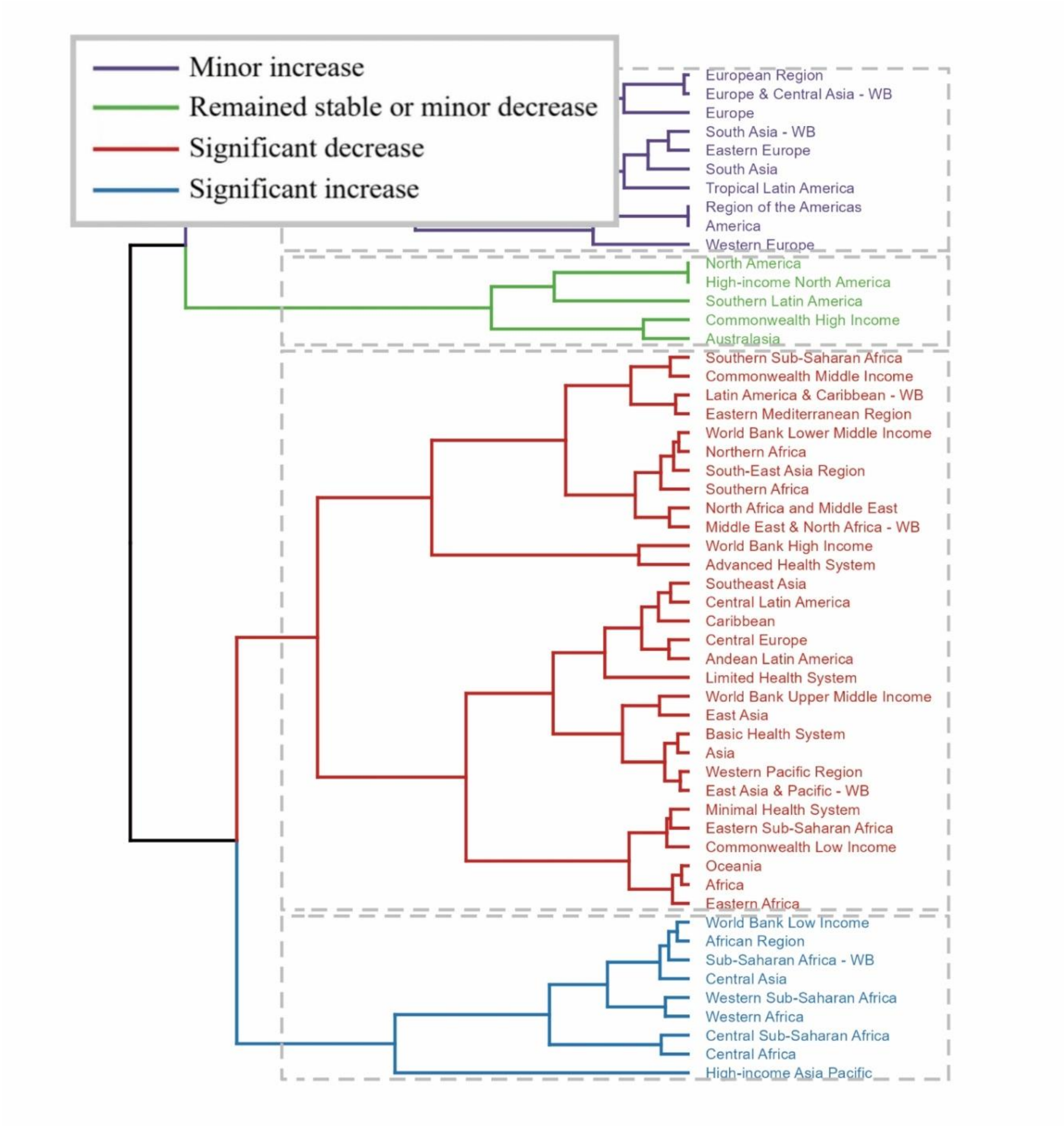

Figure 5: Results of cluster analysis based on the EAPC values of LCHB-related age-standardized rates for deaths, DALYs, incidence, prevalence from 1990 to 2021.
Abbreviations: EAPC, estimated annual percentage change.

3.3 Factors Influencing EAPC

We further examined the relationship between the EAPC in ASR from 1990 and the Human Development Index (HDI) in 2021, using the 1990 ASR as the baseline for disease prevalence. Our analysis revealed a negative correlation between EAPCs and ASR when ASR values were relatively low. Conversely, when ASR values were high, the association between EAPCs and ASR reversed, though this reversal was not statistically significant. Additionally, we observed a significant positive correlation between EAPCs and HDI. Specifically, from 1990 to 2019, countries with higher HDI experienced a marked increase in the growth rate of ASR for LCHB (**Figure 4C**).

3.4 ASR-based Correlation Analysis

We found an inverse relationship between the SDI and ASR across different GBD regions. Specifically, as SDI increased, ASRs of incidence, prevalence, mortality, and DALY showed a decreasing trend (**Figure 6A**).

At the country level, the relationship between SDI and ASR was more nuanced. Initially, ASR rose with increasing SDI until an SDI of approximately 0.25. Beyond this point, ASR decreased as SDI increased from 0.25 to 0.5. Between SDI values of 0.5 and 0.55, ASRs increased slowly. Beyond an SDI of 0.55, ASRs showed decreasing trends with higher SDI values and stabilized over time. Notably, after an SDI surpasses 0.75, ASRs of incidence and prevalence began to increase again, suggesting that countries with very high SDIs tend to experience higher LCHB incidence and prevalence rates (**Figure 6B**).

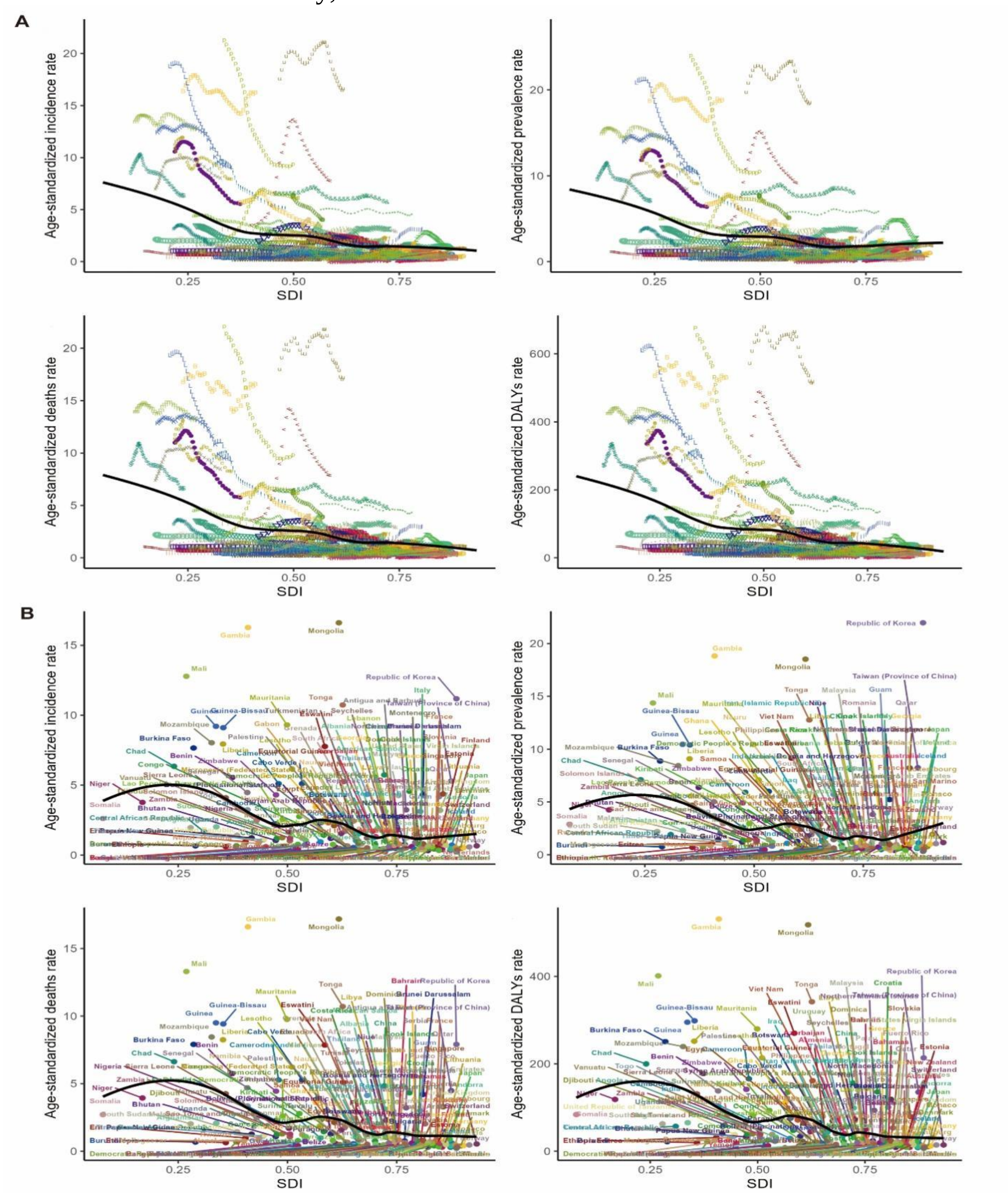

Figure 6: Age-standardized rates of incidence, prevalence, deaths and DALYs attributable to LCHB across countries and territories by soci-demographic index for both sexes, 1990 -2021(A-B). The black line was an adaptive association fitted with adaptive Loess regression based on all data points. Abbreviations: SDI, socio-demographic index.

3.5 Predictions from 2022 to 2050

Predictions from the ARIMA model suggest that between 2022 and 2050, the number of LCHB incidence cases, prevalence cases, deaths, and DALYs will rise for both sexes. However, ASRs are anticipated to remain relatively stable. Notably, ASRs of mortality and DALY are projected to decline for females over this period (**Figure 7A**).

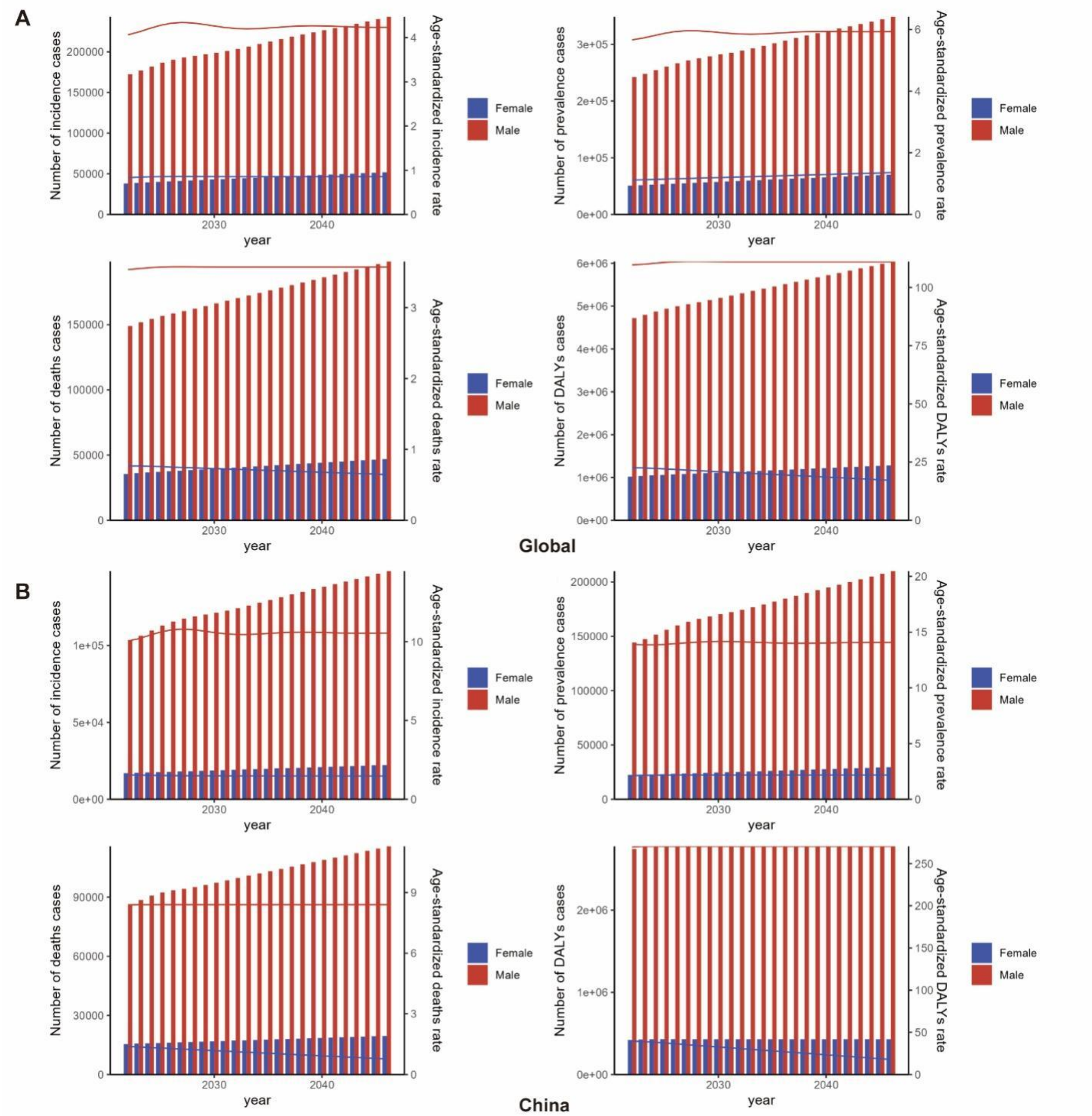

Figure7: The predicted results in the LCHB-related numbers and age-standardized rates of ASIR, ASPR, ASDR and ASR of DALYs by sex globally(A) and China(B) from 2022 to 2050 of the ARIMA model.

3.6 The Frontier Analysis Shows an Inverse Relationship Between SDI and ASR

The effective variance (EF) associated with a given SDI decreased as the SDI increased, stabilizing when the SDI exceeded 0.3. This pattern highlights the unrealized health gains from 1990 to 2021 across regions or countries at various stages of development. The EF in morbidity, mortality, prevalence, and DALYs burdens in 2021 across countries or regions with different levels of sociodemographic development. Generally, the EF diminished as sociodemographic development progressed, indicating that regions with lower SDIs had less potential for further burden reduction (**Figures 8A-H**).

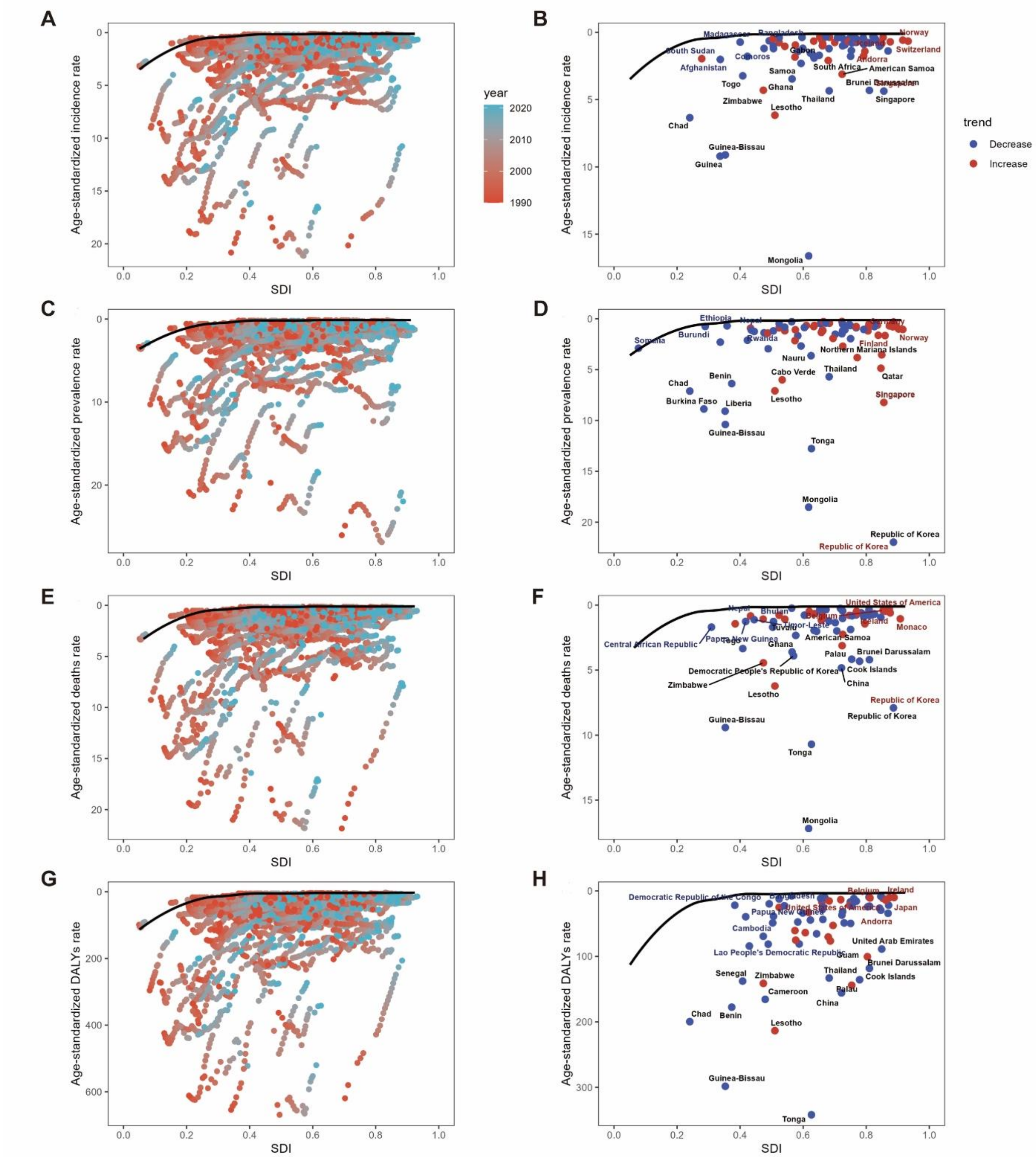

Figure 8: Frontier analysis involving SDI and LCHB disease burden in 2021.
(A-B) Frontier analysis with ASIR. (C-D) Frontier analysis with ASPR. (E-F) Frontier analysis with ASDR. (G-H) Frontier analysis with ASR of DALYs. The frontier is marked using a solid black color, and countries and territories are presented as dots. The leading 15 countries with the most EF (the highest ASIR of LCHB gap from frontier) are marked in black. Examples of frontier countries with low SDI (<0.5) and reduced EF are marked in blue, and those with high SDI (>0.85) and relatively elevated EF for their development are marked in red. Blue dots represent a reduction in LCHB burden between 1990 and 2021.
Abbreviations: ASIR, age-standardized incidence rate; ASPR, age-standardized prevalence rate; ASDR, age-standardized deaths rate; EF, effective difference; SDI, socio-demographic index.

3.7 Liver Cancer Burden in China - 2021

In 2021, the number of LCHB incidence, prevalence, deaths and DALYs in China was 118,665 cases, 165,217 cases, 100,194 cases and 3,148,553 cases respectively, accounting for 57.5%, 55.3%, 80.1% and 55.5% of the world population. Consistent with global trends, the

ASRs for incidence, prevalence, mortality, and DALYs in China also increased with age up to a certain point before declining. Specifically, ASRs of incidence peaked in the 85–89 age group, ASRs of prevalence in the 65-69 age group, ASRs of mortality in the 90-94 age group, and ASRs of DALYs in the 60-64 age group, showing slight variations from global peak ages. The highest counts were observed in the 50-54 age group for incidence (17,684 cases), prevalence (26,633 cases), and DALYs (511,484 cases), while the highest number of deaths was in the 65-69 age group (13,862 cases) (**Figure 9A， Tables 5-8**).

Table 5: Number of deaths and age-standardized deaths rates due to LCHB in 1990 and 2021, and trends in China from 1990 to 2021.

Characteristics	Number of deaths cases (95% UI) in 1990	The age-standardized deaths rate/100000 (95% UI) in 1990	Number of deaths cases (95% UI) in 2021	The age-standardized deaths rate/100000 (95% UI) in 2021	EAPC (95% CI)
China	61,415 (50,743-73,122)	6.53 (5.42-7.76)	100,194 (77,721-129,138)	4.83 (3.76-6.19)	-0.97 (-1.15--0.79)
Female	9,890 (7,690-12,251)	2.18 (1.7-2.7)	15,129 (11,159-19,856)	1.4 (1.04-1.84)	-1.37 (-1.52--1.23)
Male	51,524 (41,305-62,899)	10.96 (8.85-13.33)	85,065 (63,905-114,760)	8.48 (6.42-11.29)	-0.82 (-1.01--0.63)
10-14 years	177 (144-219)	0.17 (0.14-0.21)	57 (45-76)	0.07 (0.05-0.09)	-3.62 (-4.19--3.04)
15-19 years	264 (216-327)	0.21 (0.17-0.26)	78 (61-102)	0.1 (0.08-0.14)	-2.69 (-3.1--2.27)
20-24 years	642 (515-788)	0.49 (0.39-0.6)	205 (144-283)	0.28 (0.2-0.39)	-3.12 (-3.62--2.61)
25-29 years	1,258 (1,019-1,566)	1.14 (0.93-1.43)	759 (596-949)	0.88 (0.69-1.1)	-1.77 (-2.49--1.04)
30-34 years	2,503 (2,069-3,053)	2.84 (2.34-3.46)	2,490 (1,919-3,256)	2.05 (1.58-2.69)	-1.82 (-2.36--1.28)
35-39 years	4,419 (3,623-5,411)	4.84 (3.97-5.92)	3,771 (2,842-5,042)	3.56 (2.68-4.76)	-1.47 (-1.74--1.2)
40-44 years	6,259 (5,001-7,705)	9.33 (7.45-11.48)	5,571 (4,168-7,455)	6.09 (4.55-8.14)	-1.81 (-2.03--1.59)
45-49 years	6,765 (5,279-8,298)	13.11 (10.23-16.08)	9,759 (7,146-13,054)	8.85 (6.48-11.83)	-1.24 (-1.6--0.88)
50-54 years	7,543 (5,982-9,271)	15.81 (12.54-19.43)	13,305 (9,766-18,186)	11.01 (8.08-15.05)	-0.98 (-1.23--0.72)
55-59 years	7,944 (6,333-9,766)	18.32 (14.6-22.52)	13,149 (9,452-17,728)	11.96 (8.6-16.12)	-1.43 (-1.71--1.16)
60-64 years	7,693 (6,036-9,455)	21.77 (17.08-26.76)	11,259 (8,122-15,310)	15.42 (11.13-20.97)	-0.98 (-1.15--0.81)
65-69 years	6,665 (5,230-8,238)	24.43 (19.17-30.2)	13,862 (10,046-17,857)	18.07 (13.1-23.28)	-0.82 (-1.09--0.54)
70-74 years	4,880 (3,781-6,114)	25.93 (20.09-32.49)	10,257 (7,494-13,712)	19.25 (14.06-25.73)	-1.25 (-1.54--0.97)
75-79 years	2,765 (2,214-3,443)	24.29 (19.45-30.25)	6,918 (5,239-9,001)	20.89 (15.82-27.18)	-0.47 (-0.81--0.12)
80-84 years	1,089 (858-1,347)	20.57 (16.2-25.43)	5,121 (3,832-6,785)	25.87 (19.36-34.28)	1.82 (1.35-2.28)
85-89 years	472 (377-594)	27.99 (22.32-35.19)	2,693 (2,047-3,516)	28.27 (21.49-36.91)	0.6 (0.3-0.91)
90-94 years	73 (56-96)	23.91(18.26-	838 (604-1,153)	28.57 (20.6-39.34)	0.68 (0.38-0.9 9

		31.21)			)
95+ years	4 (2-5)	8.9 (5.64-12.6)	103 (64-152)	16.08 (9.99-23.75)	2.69 (2.35-3.0 3)

Table 6: Number of DALYs and age-standardized DALYs rates due to LCHB in 1990 and 2021, and trends in China from 1990 to 2021.

Characteristics	Number of DALYs cases (95% UI) in 1990	The age-standardized DALYs rate/100000 (95% UI) in 1990	Number of DALYs cases (95% UI) in 2021	The age-standardized DALYs rate/100000 (95% UI) in 2021	EAPC (95% CI)
China	2,236,077 (1,842,616-2,663,358)	220.05 (181.34-260.91)	3,148,553 (2,442,865-4,109,014)	155.81 (121.32-201.99)	-1.22 (-1.41--1.03)
Female	335,318 (264,347-410,310)	68.37 (54.05-84.2)	415,170 (306,814-554,410)	39.71 (29.57-52.76)	-1.87 (-2.04--1.69)
Male	1,900,759 (1,528,585-2,319,159)	365.38 (293.8-446.15)	2,733,383 (2,046,835-3,699, 193)	271.87 (204.97-364.75)	-1.04 (-1.24--0.85)
10-14 years	13,752 (11,215-16,994)	13.44 (10.96-16.61)	4,458 (3,460-5,923)	5.17 (4.01-6.87)	-3.62 (-4.19--3.04)
15-19 years	19,230 (15,733-23,748)	15.18 (12.42-18.75)	5,690 (4420-7419)	7.62 (5.92-9.94)	-2.69 (-3.1--2.27)
20-24 years	43,614 (34,990-53,518)	33.04 (26.51-40.54)	13,888 (9,756-19,191)	18.98 (13.33-26.23)	-3.12 (-3.62--2.62)
25-29 years	79,455 (64,371-98,850)	72.3 (58.58-89.95)	47,751 (37,471-59,744)	55.22 (43.33-69.08)	-1.77 (-2.49--1.04)
30-34 years	144,674 (119,682-176,531)	163.95 (135.63-200.05)	144,266 (111,324-188,682)	119.08 (91.89-155.74)	-1.81 (-2.35--1.27)
35-39 years	234,441 (192,146-287,216)	256.67 (210.37-314.45)	200,584 (151,476-268,669)	189.3 (142.95-253.55)	-1.47 (-1.75--1.19)
40-44 years	301,327 (240,691-370,832)	449.11 (358.73-552.7)	268,178 (200,828-358,357)	292.98 (219.4-391.5)	-1.82 (-2.04--1.6)
45-49 years	292,217 (228,048-358,513)	566.1 (441.79-694.54)	421,036 (308,164-562,820)	381.64 (279.33-510.16)	-1.24 (-1.6--0.88)
50-54 years	289,389 (229,238-356,177)	606.55 (480.47-746.53)	511,484 (375,387-698,779)	423.21 (310.6-578.18)	-0.97 (-1.23--0.7)
55-59 years	268,152 (213,709-329,639)	618.3 (492.77-760.08)	445,073 (320,000-600,520)	404.82 (291.06-546.21)	-1.43 (-1.71--1.15)
60-64 years	223,917 (175,809-275,083)	633.65 (497.51-778.45)	327,271 (236,359-444,891)	448.29 (323.76-609.4)	-0.98 (-1.16--0.81)
65-69 years	163,253 (128,079-201,909)	598.39 (469.47-740.09)	339,654 (246,336-437,801)	442.81 (321.15-570.77)	-0.81 (-1.08--0.53)
70-74 years	98,482 (76,152-123,306)	523.35 (404.68-655.27)	207,289 (151,750-277,253)	388.94 (284.73-520.21)	-1.25 (-1.53--0.97)
75-79 years	44,858 (35,828-55,759)	394.16 (314.81-489.94)	111,860 (84,578-146,000)	337.75 (255.38-440.84)	-0.48 (-0.83--0.14)
80-84 years	13,860 (10,904-17,118)	261.65 (205.85-323.16)	64,730 (48,367-85,815)	327.05 (244.38-433.59)	1.8 (1.33-2.27)
85-89 years	4,783 (3,808-5,998)	283.52 (225.75-355.58)	27,144 (20,634-35,422)	284.95 (216.61-371.86)	0.59 (0.29-0.9)
90-94 years	645 (493-842)	210.13 (160.63-274.38)	7,350 (5,303-10,134)	250.68 (180.86-345.65)	0.68 (0.37-0.98)
95+ years	30 (19-43)	74.22 (47.03-105.22)	849 (526-1,254)	132.77 (82.34-196.23)	2.67 (2.32-3.02)

Table 7: Number of incidence and age-standardized incidence rates due to LCHB in 1990 and 2021, and trends in China from 1990 to 2021.

Characteristics	Number of incidence cases (95% UI) in 1990	The age-standardized incidence rate/100000 (95% UI) in 1990	Number of incidence cases (95% UI) in 2021	The age-standardized incidence rate/100000 (95% UI) in 2021	EAPC (95% CI)
China	63,118 (52,018-75,227)	6.58 (5.45-7.84)	118,665 (92,280-153,556)	5.73 (4.48-7.38)	-0.42 (-0.58--0.26)
Female	9,911 (7,731-12,322)	2.14 (1.67-2.66)	16,822 (12,386-22,197)	1.56 (1.16-2.07)	-0.99 (-1.12--0.87)
Male	53,208 (42,645-65,059)	11.01 (8.88-13.4)	101,843 (76,298-137,861)	10.04 (7.6-13.49)	-0.25 (-0.41--0.09)
10-14 years	170 (138-210)	0.17 (0.14-0.21)	66 (51-88)	0.08 (0.06-0.1)	-3.02 (-3.52--2.51)
15-19 years	271 (222-335)	0.21 (0.18-0.26)	98 (76-129)	0.13 (0.1-0.17)	-2.01 (-2.35--1.67)
20-24 years	634 (511-782)	0.48 (0.39-0.59)	248 (176-340)	0.34 (0.24-0.47)	-2.52 (-2.98--2.06)
25-29 years	1,361 (1,102-1,692)	1.24 (1-1.54)	1,005 (786-1,256)	1.16 (0.91-1.45)	-1.13 (-1.81--0.44)
30-34 years	2,745 (2,264-3,336)	3.11 (2.57-3.78)	3,331 (2,607-4,313)	2.75 (2.15-3.56)	-1.17 (-1.65--0.69)
35-39 years	5,109 (4,178-6,321)	5.59 (4.57-6.92)	5,306 (4,025-7,136)	5.01 (3.8-6.73)	-0.88 (-1.14--0.61)
40-44 years	6,942 (5,542-8,581)	10.35 (8.26-12.79)	7,716 (5,753-10,324)	8.43 (6.29-11.28)	-1.03 (-1.25--0.81)
45-49 years	7,337 (5,742-9,074)	14.21 (11.12-17.58)	13,260 (9,710-17,824)	12.02 (8.8-16.16)	-0.41 (-0.76--0.06)
50-54 year	8,063 (6,375-9,907)	16.9 (13.36-20.76)	17,684 (12,977-23,973)	14.63 (10.74-19.84)	-0.12 (-0.37-0.13)
55-59 years	8,200 (6,495-10,060)	18.91 (14.98-23.2)	16,140 (11,617-21,821)	14.68 (10.57-19.85)	-0.86 (-1.06--0.67)
60-64 years	7,733 (6,079-9,508)	21.88 (17.2-26.91)	13,306 (9,558-18,095)	18.23 (13.09-24.79)	-0.4 (-0.57--0.23)
65-69 years	6,425 (5,042-7,960)	23.55 (18.48-29.18)	15,334 (11,157-19,933)	19.99 (14.55-25.99)	-0.32 (-0.57--0.06)
70-74 years	4,469 (3,471-5,591)	23.75 (18.45-29.71)	10,769 (7,844-14,483)	20.21 (14.72-27.17)	-0.81 (-1.06--0.56)
75-79 years	2,380 (1,905-2,962)	20.92 (16.74-26.03)	6,710 (5,046-8,760)	20.26 (15.24-26.45)	-0.1 (-0.4-0.2)
80-84 years	871 (682-1,074)	16.43 (12.88-20.28)	4,575 (3,415-6,073)	23.12 (17.26-30.68)	2.3 (1.81-2.79)
85-89 years	357 (286-447)	21.19 (16.98-26.5)	2457 (1,861-3,209)	25.8 (19.53-33.69)	1.23 (0.94-1.52)
90-94 years	50 (38-65)	16.29 (12.42-21.22)	595 (429-815)	20.28 (14.63-27.81)	0.92 (0.59-1.25)
95+ years	2 (1-3)	5.54 (3.51-7.85)	65 (40-97)	10.23 (6.33-15.11)	3.07 (2.66-3.48)

Table 8: Number of prevalence and age-standardized prevalence rates due to LCHB in 1990 and 2021, and trends in China from 1990 to 2021.

Characteristics	Number of prevalence cases (95% UI) in 1990	The age-standardized prevalence rate/100000 (95% UI) in 1990	Number of prevalence cases (95% UI) in 2021	The age-standardized prevalence rate/100000 (95% UI) in 2021	EAPC (95% CI)
China	80,153 (65,848-95,282)	7.97 (6.55-9.46)	165,217 (129,037-215,080)	8.08 (6.33-10.47)	0.04 (-0.13-0.21)
Female	12,069 (9,476-14,878)	2.49 (1.96-3.08)	22,213 (16,283-29,350)	2.12 (1.56-2.79)	-0.54 (-0.71--0.38)
Male	68,083 (54,677-83,283)	13.27 (10.66-16.18)	143,004 (107,414-193,163)	14.08 (10.66-18.83)	0.21 (0.04-0.38)
10-14 years	316 (257-392)	0.31 (0.25-0.38)	132 (102-176)	0.15 (0.12-0.2)	-2.77 (-3.27--2.26)
15-19 years	452 (370-558)	0.36 (0.29-0.44)	175 (137-229)	0.23 (0.18-0.31)	-1.78 (-2.1--1.45)
20-24 years	1,003 (811-1,235)	0.76 (0.61-0.94)	420 (299-571)	0.57 (0.41-0.78)	-2.29 (-2.75--1.83)
25-29 years	3,212 (2,598-3,994)	2.92 (2.36-3.63)	2,541 (1,983-3,177)	2.94 (2.29-3.67)	-0.9 (-1.59--0.2)
30-34 years	5,768 (4,759-7,010)	6.54 (5.39-7.94)	7,431 (5,831-9,613)	6.13 (4.81-7.93)	-0.97 (-1.46--0.49)
35-39 years	8,587 (7,023-10,624)	9.4 (7.69-11.63)	9,563 (7,266-12,839)	9.02 (6.86-12.12)	-0.65 (-0.92--0.38)
40-44 years	8,897 (7,098-11,003)	13.26 (10.58-16.4)	11,646 (8,700-15,402)	12.72 (9.5-16.83)	-0.48 (-0.71--0.25)
45-49 years	9,455 (7,410-11,683)	18.32 (14.36-22.63)	20,220 (14,791-27,111)	18.33 (13.41-24.57)	0.16 (-0.18-0.5)
50-54 years	10,223 (8,088-12,569)	21.43 (16.95-26.34)	26,633 (19,581-36,079)	22.04 (16.2-29.85)	0.48 (0.23-0.73)
55-59 years	10,020 (7,939-12,292)	23.1 (18.3-28.34)	23,239 (16,610-31,556)	21.14 (15.11-28.7)	-0.28 (-0.46--0.09)
60-64 years	8,643 (6,791-10,631)	24.46 (19.22-30.08)	18,136 (13,071-24,648)	24.84 (17.9-33.76)	0.29 (0.11-0.47)
65-69 years	6,708 (5,262-8,307)	24.59 (19.29-30.45)	19,420 (14,159-25,426)	25.32 (18.46-33.15)	0.35 (0.08-0.61)
70-74 years	4,043 (3,142-5,057)	21.48 (16.7-26.88)	12,038 (8,751-16,082)	22.59 (16.42-30.17)	-0.08 (-0.3-0.15)
75-79 years	1,953 (1,562-2,432)	17.16 (13.73-21.37)	6,924 (5,211-9,047)	20.9 (15.73-27.32)	0.68 (0.4-0.95)
80-84 years	625 (490-773)	11.8 (9.24-14.59)	4,322 (3,196-5,808)	21.84 (16.15-29.35)	3.29 (2.81-3.77)
85-89 years	219 (175-274)	12.96 (10.39-16.24)	1,985 (1,521-2,603)	20.84 (15.96-27.33)	2.17 (1.91-2.44)
90-94 years	28 (21-36)	9.07 (6.92-11.82)	361 (260-496)	12.3 (8.88-16.91)	1.21 (0.9-1.52)
95+ years	1 (1-2)	2.78 (1.76-3.95)	33 (20-49)	5.18 (3.2-7.65)	3.09 (2.68-3.5)

Similar to global patterns, Chinese males experienced a significantly higher burden of LCHB compared to females in 2021. ASRs of incidence, prevalence, mortality, and DALYs for males were 6.44, 6.64, 6.00, and 6.85 times higher, respectively than those for females. Specifically, the number of incidence cases in males was 101,843, and the number of deaths was 85,065, which were 6.05 and 5.62 times higher than the respective figures for females (16,822 incidence cases and 15,129 deaths). These figures exceeded the global male-to-female ratios for incidence and mortality (4.87 and 4.22 times higher, respectively). In addition, males had 143,004 prevalent cases and 2,733,383 DALYs, which were 6.44 and 6.58 times higher than the female figures (22,213 prevalent cases and 415,170 DALYs) (**Figure 9B**).

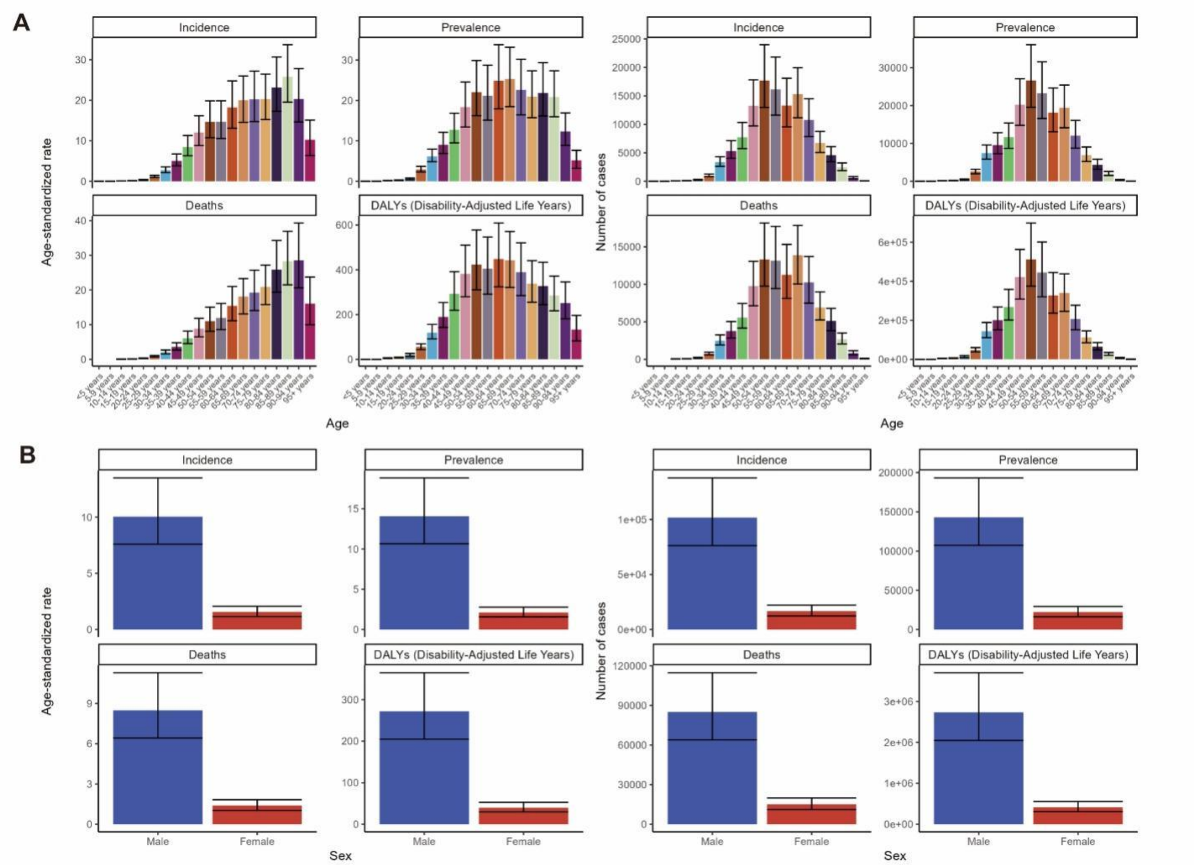

Figure 9: The number of LCHB-related deaths, DALYs, incidence, and prevalence in China by age group (A) and sex (B) and the corresponding age-standardized rates in 2021.

3.8 Trends in the LCHB Burden in China From 1990 to 2021

Between 1990 and 2021, China experienced significant increases in LCHB burden. The number of incidence cases rose from 63,118 to 118,665, deaths from 61,415 to 100,194, prevalence from 80,153 to 165,217, and DALYs from 2,236,077 to 3,148,553. Notably, ASRs for incidence, deaths, and DALYs showed an overall decreasing trend (EAPC for incidence: -0.42 [95% CI: -0.58 to -0.26]; deaths: -0.97 [95% CI: -1.15 to -0.79]; DALYs: -1.22 [95% CI: -1.41 to -1.03]), whereas the ASR for prevalence showed a slight increase (EAPC: 0.04 [95% CI: -0.13 to 0.21]), reflecting global patterns of LCHB burden **(Figure 10A, Tables 5-8)**.

At the age level, ASRs of incidence, prevalence, and mortality generally decreased from 1990 to 2021. The 10-14 age group experienced the most significant reductions in ASRs of incidence (EAPC: -3.02 [95% CI: -3.52 to -2.51]), prevalence (EAPC: -2.77 [95% CI: -3.27 to -2.26]), mortality (EAPC: -3.62 [95% CI: -4.19 to -3.04]), and DALYs (EAPC: -3.62 [95% CI: -4.19 to -3.04]). Conversely, the over-95 years age group saw the greatest increases in age-standardized incidence (EAPC: 3.07 [95% CI: 2.66 to 3.48]), prevalence (EAPC: 3.09 [95% CI: 2.68 to 3.50]), mortality (EAPC: 2.69 [95% CI: 2.35 to 3.03]), and DALYs (EAPC: 2.67 [95% CI: 2.32 to 3.02]) **(Figure 10B, Tables 5-8)**. Trends in the number of specific cases in most age groups followed the pattern of change in the ASRs.

Gender-specific data align with global trends, ASRs of incidence, mortality, and DALY decreased in both sexes, although males experienced a slight increase in ASR of prevalence (EAPC: 0.21 [95% CI: 0.04 to 0.38]). The downward trend was more pronounced in females. However, the absolute numbers of incidence, prevalence, deaths, and DALYs increased annually for both sexes (**Figure 10C**).

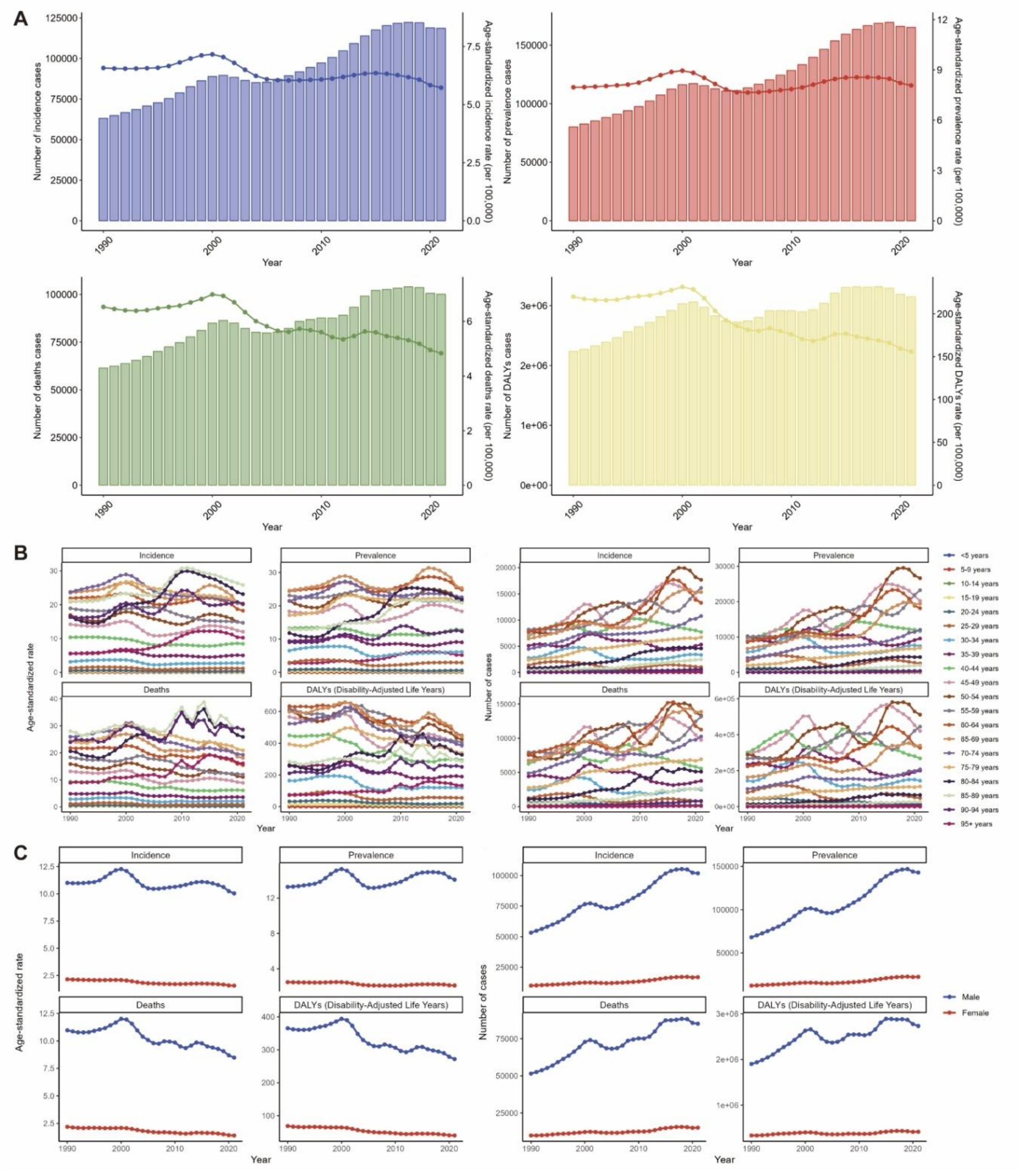

Figure 10: Temporal trend for LCHB-related disease burden from 1990 to 2021.
(B-D) Time trends in the global burden of disease associated with LCHB, 1990-2021 (A), and by age group (B), gender (C), and SDI region (D).

3.9 Predictions for China from 2022 to 2050

Consistent with global projections, the ARIMA model forecasts that from 2022 to 2050, the number of incidence cases, prevalence cases, and deaths related to LCHB in China will continue to rise for both sexes. However, the number of DALYs is expected to stabilize. The ASRs for these metrics are anticipated to remain relatively stable overall. Notably, ASRs of mortality and DALYs for females are projected to decline over this period (**Figure 7B**).

3.10 Risk factors for LCHB

We analyzed the impact of four risk factors on global and Chinese mortality rates and DALYs due to HCC from 1990 to 2021. On a global scale, smoking was the predominant risk factor for HCC-related deaths and DALYs, while drug use had a relatively minor effect. Although smoking's contribution to HCC mortality and DALYs declined over the years—from 74.9% in 1990 to 54.0% in 2021—it remained the primary risk factor, with the ASR reflecting this trend. In contrast, the impact of high body mass index (BMI) on HCC steadily increased, with its contribution rising from 15.5% in 1990 to 34.6% in 2021. Trends in China mirrored global patterns, as shown in **Figure 11A-D**.

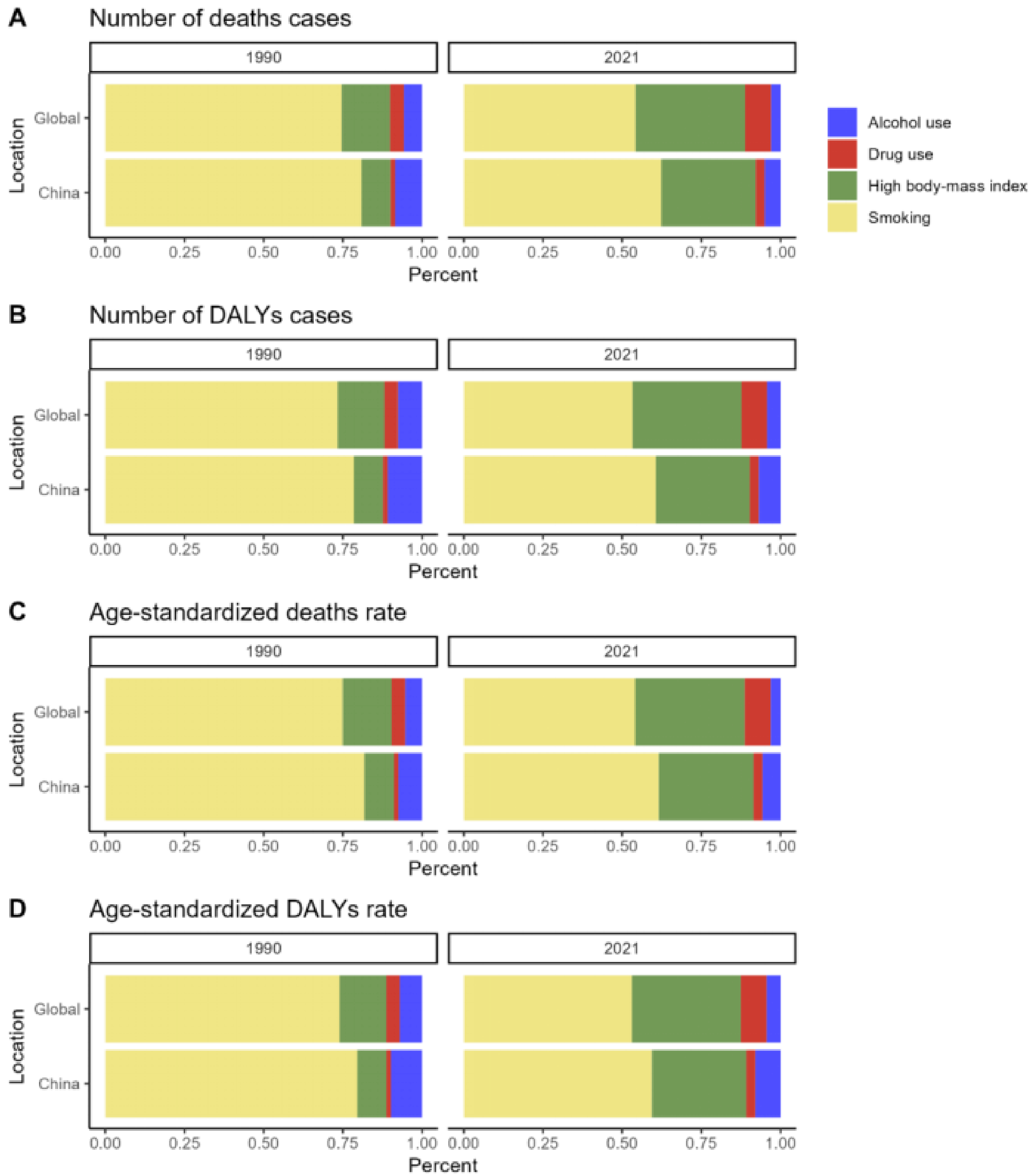

Figure 11: Analysis of LCHB-related risk factors.

4. Discussion

To the best of our knowledge, this is the first comprehensive study to evaluate the global and Chinese burden of LCHB, detailing trends and making future projections. In 2021, LCHB represented a significant global health burden, with considerable variation by gender, age, SDI region, GBD region, and country. Although there has been a trend toward improvement in the global ASRs from 1990 to 2021, the prevalence of LCHB remains alarmingly high and is increasing. Our forecasts indicate that over the next 30 years, the incidence, prevalence, mortality, and DALYs associated with LCHB will continue to rise.

Previous research has investigated the global burden of HCC, focusing on how various risk factors contribute to the disease. While these studies have included a broad range of risk factors, they often lack detailed analysis of each factor. Additionally, most research has been global in scope, without delving into the specifics of HCC's impact on individual countries or regions [6,7]. The burden of HCC varies significantly across different geographic areas due to differing exposure factors. For instance, Zhenqiu Liu et al. used data from the GBD 2016 study to examine the impact of various causes of morbidity on HCC incidence and trends from 1990 to 2016. They found that in 2016, over 40% of HCC cases worldwide were attributable to HBV. Incidence rates and trends differed markedly across regions, with ASRs of HCC declining in low and intermediate SDI regions due to reduced hepatitis B incidence while increasing in medium and high SDI regions where hepatitis B prevalence remained high [6]. Likewise, Sungchul Choi et al., using GBD 2019 data, highlighted that the burden of HCC was particularly high in HBV-endemic regions and noted significant variations in the burden and trends across different countries [7]. However, these studies are somewhat outdated and lack recent updates. Moreover, specific analysis of HBV-associated HCC, the most significant risk factor for the disease, remains limited. For example, Jie Wei et al. mainly analyzed HCV-associated HCC [8]. Chunlong Liu et al. explored HCC caused by non-alcoholic fatty liver disease (NALD) [9]. Our current study addresses this gap by comprehensively evaluating the global and Chinese burden of HCC due to HBV. By integrating findings from previous studies, our research underscores the substantial contribution of HBV infection to the global HCC disease burden.

Between 1990 and 2021, there has been a noticeable decline in the incidence of LCHB, as well as in related deaths and the ASRs for DALYs. This trend is primarily attributed to the widespread adoption of HBV vaccination and the availability of anti-HBV medications [1]. For instance, China has implemented several effective measures, such as offering "free HBV vaccinations" for all newborns [10] and providing antiviral treatments for HBV patients. These initiatives have significantly reduced HBV infections and, consequently, the incidence of HCC in the general population. Nevertheless, despite these advances, the prevalence of LCHB is rising, particularly in countries with medium to high SDI levels. This increase is partly due to the growth of Asian immigrant populations and the expanding number of patients with type 2 diabetes mellitus, which is often associated with HBV due to lifestyle changes [11, 12, 13,14]. The rise in cases highlights the need for more robust HBV prevention and screening efforts in these regions.

To address the ongoing challenge, universal screening for hepatitis B should be advocated globally. According to Polaris, only 14% of HBV cases are diagnosed worldwide, with an even lower treatment rate of 8% [15]. Expanding screening programs has been shown to increase treatment rates and reduce mortality [16-22]. Furthermore, implementing universal hepatitis B vaccination programs for all age groups, rather than just high-risk populations, is crucial [23,24]. Effective antiviral treatments are also essential for preventing the progression of hepatitis B to liver cancer and for improving long-term patient outcomes [25].

The current study reveals that men experience a significantly higher burden of LCHB compared to women—a finding not prominently featured in previous research. Specifically, men are 4-5 times more likely than women to develop LCHB, exhibit higher prevalence rates, and suffer greater mortality. This disparity may be attributed to several factors, including higher exposure to risk behaviors such as smoking, drug use, and high-risk sexual practices, which can exacerbate liver damage, increase HBV transmission, and heighten susceptibility to HCC. Additionally, some studies suggest that androgens may contribute to a higher risk of liver cancer following HBV infection due to their immunosuppressive effects [26-28]. Furthermore, men’s generally lower health awareness and the asymptomatic nature of early-stage HCC often result in delayed diagnosis and more advanced disease at presentation, contributing to higher mortality rates among men with LCHB. This significant gender disparity underscores the need for further research into the underlying mechanisms.

Age is another critical risk factor for LCHB, with the highest incidence observed in individuals over 70 years of age [1, 29]. Our study corroborates previous findings, showing that LCHB mortality peaked in 2021 among those aged 85-89 years, with the most substantial increases in age-standardized incidence and mortality rates occurring in individuals over 90 years from 1990 to 2021. Li et al. attributed the heightened risk in older adults to the longer duration of HBV infection and the prevalence of age-related comorbidities [30]. Early diagnosis and effective treatment, supported by robust screening programs, are crucial for reducing mortality among the elderly population.

Geographical disparities in the burden of LCHB are also significant, with variations across different regions and countries due to diverse environments, healthcare systems, and levels of economic development [6, 9]. LCHB is more prevalent in regions with low to moderate SDI, such as HBV-endemic areas in East Asia and sub-Saharan Africa. Despite improvements in HBV vaccination and efforts towards the World Health Organization's goal of "eliminating viral hepatitis by 2030" [1], these regions continue to experience high prevalence and mortality rates. Conversely, high SDI countries, including the UK, Poland, and Australia, have seen a rapid rise in LCHB incidence and mortality, highlighting the need for intensified interventions in these areas. Overall, LCHB remains a major public health concern, particularly in developing countries, while its impact is growing in some developed nations. Our study confirms that the burden of LCHB is highest in medium-SDI regions and is increasing in medium-high and high-SDI areas.

Projections indicate that globally, both the number of LCHB cases and related deaths will rise from 2022 to 2050, though ASRs are expected to remain relatively stable. This anticipated increase in disease burden is likely due to demographic changes, rising high-risk behaviors, and socioeconomic development. Therefore, enhancing tertiary prevention measures is critical for mitigating the disease burden.

Asia, particularly China, accounts for the highest incidence of liver cancer, with GLOBOCAN 2022 reporting that 70.1% of global cases occur in Asia, and China alone contributes 60.5% of the region's incidence [1]. HBV remains the leading cause of liver cancer in China, responsible for 92.05% of cases [2]. Although the incidence of liver cancer in China has been declining since the 1990s [1,31], largely due to HBV vaccination [32], the absolute number of cases and deaths remains high, and the ASR for prevalent cases continues to rise. Contributing factors include low diagnosis and treatment rates despite increased public health interventions [33], and an aging population, with the elderly being at higher risk for liver cancer and more likely to have comorbid conditions that exacerbate the disease [3, 34].

This study's strengths lie in its comprehensive analysis of the latest global and national data on HBV-related HCC, including incidence, prevalence, mortality, and DALYs, and its use of ARIMA models for future predictions. However, limitations include reliance on GBD 2021 data, which may suffer from accuracy issues due to the quality and scope of input data, and a lack of detailed information on factors like vaccination policies and antiviral treatment. Moreover, projections assume constant future conditions, though real-world variables may change. Further research is needed to refine these estimates and address the complexities of HBV-related liver cancer.

5. Conclusion

In conclusion, LCHB remains a significant global public health challenge. Although the ASR for LCHB has decreased, reflecting notable advancements in prevention efforts, the absolute number of cases is still rising, highlighting the persistent and substantial burden of the disease. Regionally, the burden of LCHB varies markedly: countries with medium levels of economic development, such as those in Asia and East Asia and the Pacific, experience the highest rates, while developed nations like Australia and Qatar have seen increasing ASRs. Additionally, LCHB disproportionately affects males and the elderly. Our projections indicate that the number of LCHB cases will continue to rise both globally and within China over the next 25 years. This underscores the need for more robust and targeted prevention and treatment strategies to effectively combat this ongoing public health issue.

Contributors

Qianzi Kou and Ying Li managed the overall research enterprise and wrote the first draft of the manuscript. They also held primary responsibility for applying analytical methods to generate estimates.

Qianzi Kou was primarily responsible for seeking, cataloguing, extracting, and cleaning data, as well as designing and coding figures and tables. Sophearin Rith, Pengkhun Nov, Jiqiang Li contributed by providing data or offering critical feedback on data sources, along with Pengkhun Nov, Jiqiang Li.

Data Sharing

This study adheres to the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER). To access the data used in these analyses, please visit the Global Health Data Exchange (GHDx) at https://ghdx.healthdata.org/gbd-2021.

Declaration of Interests

We affirm that we have no financial or personal relationships with individuals or organizations that could improperly influence our work. Additionally, we have no professional or personal interests of any kind in any product, service, or company that might be perceived as affecting the positions presented in or the review of the manuscript entitled.

Ethics Approval

Not applicable.

Patient Consent for Publication

Not applicable.

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