Original Article

Burden of Liver Cancer Attributable to Hepatitis B and Alcohol Globally, in China, and for Five Sociodemographic Index Regions from 1990 to 2021: A Population-based Study

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Abstract

Background and Aims: Liver cancer is a digestive system malignancy that poses a significant public health challenge globally. This study aimed to analyze and compare the epidemiological trends of liver cancer attributed to hepatitis B (LCHB) and alcohol use (LCAL) over the past 32 years. ***Methods:*** Data on mortality and disability-adjusted life years for LCHB and LCAL in China, globally, and across five sociodemographic index regions were obtained from the Global Burden of Disease 2021 database and comprehensively analyzed. ***Results:*** In 2021, the global and Chinese death counts and disability-adjusted life years attributed to LCHB and LCAL showed substantial increases compared to 1990. China had the highest number of deaths from LCHB and LCAL among 204 countries and regions. Gender and age disparities were notable, with males and those aged 40–75 years bearing a higher burden than females and other age groups. Global age-period-cohort analysis revealed an escalating risk of death from LCHB with age, alongside a lower risk in younger cohorts and more recent periods. The mortality risk for LCAL also increased with age but exhibited distinct cohort and period effects compared to LCHB. Decomposition analysis indicated that shifts in the global burden of LCHB and LCAL were influenced by population growth, with population aging playing a crucial role in China. ***Conclusions:*** A significant burden of LCHB and LCAL persists, highlighting the need for tailored prevention, screening, and control strategies to mitigate their

incidence, as well as the identification of advanced therapeutics to reduce mortality.

Introduction

Liver cancer is a significant malignancy affecting the digestive system, posing a substantial public health challenge for both global and Chinese populations.[1,2] It is characterized by high morbidity and mortality, leading to substantial health loss and a considerable economic burden.[2,3] Recent global cancer statistics for 2022 reported almost a million (865,269) new cases of liver cancer (4.3% of the total cancer burden), ranking it sixth among all malignancies and accounting for 757,948 liver cancer-related deaths (7.8% of the total cancer mortality), making it the third leading cause of cancer-related fatalities.[1] In China, data from the National Cancer Center reported 367,700 new cases of liver cancer (7.6% of the total cancer burden), ranking it fourth among all cancers, and 316,500 liver cancer-related deaths (12.3% of the total cancer mortality), ranking it second overall for cancer deaths in the same year.[4] Despite the rising incidence of non-alcoholic steatohepatitis-associated liver cancer, hepatitis B and alcohol use remain the primary etiological factors, along with hepatitis C.[3] However, there is a lack of comprehensive quantitative investigations into the latest epidemiological trends regarding the burden of liver cancer attributed to hepatitis B (LCHB) and alcohol use (LCAL) based on a high-quality data source within the same

analytical framework. This gap has impeded the development of precise public health approaches.

The recently published Global Burden of Disease Study (GBD) 2021,[5,6] led by the Institute for Health Metrics and Evaluation at the University of Washington in Seattle (USA), provides a crucial opportunity to address this knowledge gap. Understanding disease burden is essential for determining priority actions, such as tailoring public health policies, clinical interventions, and drug development, as well as assessing their subsequent effects.[7,8] Previous studies utilizing GBD data have been instrumental in shaping relevant health policies and planning.[7] For instance, Nigeria enacted a new law mandating health insurance coverage and established a vulnerable group fund for 83 million of the poorest Nigerians based on GBD data.[7]

It is important to explore how the trends of LCHB and LCAL have evolved over the past decades, as advances in cancer therapy require data spanning several years. To address this research question and bridge the current knowledge gap, our study utilized data from GBD 2021 to examine long-term epidemiological trends in LCHB and LCAL globally, in China, and across five sociodemographic index (SDI) regions from 1990 to 2021. We also analyzed the distinct impact of age, period, and birth cohort,[9,10] projecting deaths attributed to LCHB and LCAL from 2022 to 2030 in China and worldwide. These efforts aimed to enrich the existing knowledge base and provide valuable insights to inform future public health policies and clinical management strategies.

Methods

Study data

This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (Supplementary File 1).[11] GBD 2021 offers a thorough and standardized evaluation of 371 diseases and injuries, 288 causes of mortality, and 88 risk factors across age and gender globally from 1990 to 2021, covering 204 countries and territories, as well as 811 subnational regions.[5,6,12] To ensure reliable and comparable GBD data, epidemiological information from various sources was utilized to estimate disease burden using an integrative Bayesian meta-regression model, with detailed methodologies available in the GBD 2021 reports.[5,6] Our study examined data on mortality, disability-adjusted life years (DALYs), age-standardized mortality rate (ASMR), and age-standardized DALYs rate (ASDR) for LCHB and LCAL globally (204 countries and territories), in China, and across five SDI regions from 1990 to 2021. Data were sourced using the Global Health Data Exchange query tool (available at https://vizhub.healthdata.org/gbd-results/). The GBD collaborator network utilized the SDI to assess sociodemographic development, categorizing the 204 countries and territories into five groups: low (<0.466), low-middle (0.466–0.619), middle (0.619–0.712), high-middle (0.712–0.810), and high SDI (≥0.810) regions.[6] The SDI ranges from 0 to 1 and serves as a comprehensive measure based on income per person, educational attainment, and total fertility rates across all GBD study regions. A higher SDI value indicates a higher level of socioeconomic development in a country or territory, and vice versa.[6] Considering the retrospective nature of this study and the use of publicly available data, informed consent from participants was not required.

Data analysis

Statistical estimates and their 95% uncertainty intervals (UIs) for the number of deaths, DALYs, ASMRs, and ASDRs in 2019

and 2021 are reported descriptively. The UI, recommended by the GBD Collaborator Network, serves as an indicator of the certainty level of an estimate based on data availability, study size, and consistency across data sources.[13] The Joinpoint regression model was employed to compute the annual percentage change (APC) and average APC (AAPC) for ASMR and ASDR related to LCHB and LCAL globally, in China, and across the five SDI regions, evaluating the epidemiological trends from 2019 to 2021.[2] The results are presented as estimates with their 95% confidence intervals (CIs). The APC delineates trends within a specific period, while the AAPC denotes the overall trend throughout the analysis period. An upper CI bound < 0 implies a decreasing trend, while a lower CI bound > 0 indicates an increasing trend; a CI encompassing 0 suggests a stable trend. Additionally, subgroup analyses based on sex and age were conducted to further elucidate the disease burden associated with LCHB and LCAL.

Age-period-cohort analysis allows for the investigation of how age-related natural history, early-life health behaviors, contemporary medical advancements, and societal factors contribute to disease burden patterns.[9,10] In this study, we utilized an age-period-cohort framework derived from the US National Cancer Institute web-based statistical tool to differentiate the independent effects of age, period, and birth cohort on mortality attributed to LCHB and LCAL on a global scale.[14,15] The framework calculated net and local drift, representing the APC of expected age-adjusted rates and age-specific rates over the study period,[15] respectively. Key components included the longitudinal age curve to depict the age effect, the period relative risk (RR) to illustrate the period effect, and the cohort RR indicating the cohort effect.[15] The Wald chi-square test was used to assess the significance of the estimable parameters and functions. Age and period data were stratified into five-year groups, focusing on the period from 1992 to 2021 due to the 30-year analysis model restriction, with the reference age group set as 50–54 years, the reference period as 2002–2006, and the reference cohort as 1947–1956 for their proximity to the center position. Notably, as GBD 2021 lacked age data for those under 10 years for LCHB, age was segmented into eighteen five-year groups ranging from 10–14 years to 95+ years. The period of investigation was divided into six five-year intervals from 1992–1996 to 2017–2021. Furthermore, 23 partially overlapping 10-year birth cohorts were identified, from 1892–1901, 1897–1906, 1902–1911, and so on until 1992–2001, 1997–2006, and 2002–2011. Similarly, due to the absence of LCAL data in individuals under 15 years of age, age was classified into seventeen five-year groups from 15–19 years to 95+, with 22 partially overlapping 10-year birth cohorts identified, ranging from 1892–1901, 1897–1906, 1902–1911, and so on until 1987–1996, 1992–2001, and 1997–2006, while the period groups mirrored those for LCHB.

The decomposition methodology reported by Das Gupta was employed to assess the relative contributions of age structure, population growth, and epidemiological changes to the LCHB and LCAL burden in China, globally, and across the five SDI regions.[13] Disparities in DALYs for LCHB and LCAL across the 204 countries and territories were examined using the slope index and concentration index to measure absolute and relative health inequalities,[16] respectively. The study also used the integrated nested Laplace approximations framework and the Bayesian age-period-cohort model to project future mortality trends from LCHB and LCAL in China and globally.[16] Statistical analyses and chart creation were performed using R 4.4.0, Stata 12.0/SE, and Microsoft Excel 2019, with a two-tailed $p < 0.05$ considered statistically significant.

Results

LCHB burden and temporal trend

Global mortality attributable to LCHB has significantly increased over the past 32 years, with total deaths rising from 106,514 (95% UI: 91,940–124,291) in 1990 to 181,194 (95% UI: 148,896–221,685) in 2021, indicating a 70.11% surge (Table 1). However, the ASMR for LCHB demonstrated a declining trend (AAPC: −0.58%, 95% CI: −0.81%, −0.36%, $p < 0.001$) during the same period (Fig. 1A). Specifically, the ASMR per 100,000 population decreased from 2.50 (95% UI: 2.15–2.92) in 1990 to 2.09 (95% UI: 1.72–2.55) in 2021. The disease burden, measured in DALYs, also increased substantially, from 3,748,179 (95% UI: 3,255,634–4,362,511) in 1990 to 5,668,199 (95% UI: 4,706,886–6,885,071) in 2021, reflecting a 51.23% increase over the same period. The trend of ASDR for LCHB mirrored the ASMR decline (AAPC: −0.79%, 95% CI: −1.01%, −0.56%, $p < 0.001$) (Fig. 1B), with ASDR per 100,000 population dropping from 84.16 (95% UI: 73.10–97.96) in 1990 to 65.36 (95% UI: 54.43–79.35) in 2021.

In China, mortality attributable to LCHB also exhibited a notable increase, with deaths rising from 61,415 (95% UI: 50,743–73,122) in 1990 to 100,194 (95% UI: 77,721–129,138) in 2021, representing a 63.14% increase. The ASMR trend for LCHB in China showed a consistent downward pattern (AAPC: −0.93%, 95% CI: −1.35%, −0.51%, $p < 0.001$) (Fig. 1C), with ASMR per 100,000 population decreasing from 6.53 (95% UI: 5.42–7.76) in 1990 to 4.83 (95% UI: 3.76–6.19) in 2021. Correspondingly, DALYs increased from 2,236,077 (95% UI: 1,842,616–2,663,358) in 1990 to 3,148,553 (95% UI: 2,442,865–4,109,014) in 2021, reflecting a 40.81% surge. The overall trend of ASDR for LCHB also showed a decrease (AAPC: −1.07%, 95% CI: −1.52%, −0.62%, $p < 0.001$) from 1990 to 2021 (Fig. 1D), with the ASDR per 100,000 population decreasing from 220.05 (95% UI: 181.34–260.91) in 1990 to 155.81 (95% UI: 121.32–201.99) in 2021. Furthermore, as part of the high-middle SDI region, China (SDI = 0.722) had the highest number of liver cancer-related deaths (100,194; 95% UI: 77,721–129,138) compared to other countries and territories in 2021 (Fig. 2A). Over the past 32 years, as expected, deaths and DALYs attributable to LCHB increased by varying percentages across different SDI regions. Notably, the trends of ASMRs and ASDRs decreased significantly in all SDI regions except the high-middle SDI region, where the change in ASMR did not reach statistically significant levels ($p = 0.081$) (Table 1).

LCAL burden and temporal trend

Globally, total deaths due to LCAL increased from 38,172 (95% UI: 31,170–46,200) in 1990 to 92,228 (95% UI: 75,053–112,160) in 2021, indicating a 140.61% rise over the past 32 years (Table 2). The trend of ASMR for LCAL showed an upward trajectory (AAPC: 0.35%, 95% CI: 0.22%, 0.49%, $p < 0.001$) from 1990 to 2021 (Fig. 1E). Specifically, the ASMR per 100,000 population increased from 0.96 (95% UI: 0.78–1.15) in 1990 to 1.06 (95% UI: 0.86–1.29) in 2021. DALYs rose from 1,042,116 (95% UI: 852,871–1,280,544) in 1990 to 2,316,027 (95% UI: 1,887,013–2,845,789) in 2021, representing a 122.24% increase. Similarly, the ASDR for LCAL exhibited an upward trend (AAPC: 0.18%, 95% CI: 0.05%, 0.32%, $p = 0.008$) from 1990 to 2021 (Fig. 1F). Specifically, the ASDR per 100,000 population was 25.03 (95% UI: 20.59–30.5) in 1990 and increased to 26.39 (95% UI: 21.53–32.28) in 2021.

In China, the number of LCAL-related deaths increased from 7,575 (95% UI: 5,858–9,677) in 1990 to 18,317 (95% UI: 13,653–24,252) in 2021, demonstrating a 141.81% increase over the past 32 years. The trend of ASMR for LCAL remained relatively stable (AAPC: 0.00, 95% CI: −0.51%, 0.52%, $p = 0.987$) from 1990 to 2021 (Fig. 1G), with ASMRs per 100,000 population being 0.87 (95% UI: 0.69–1.10) in 1990 and 0.85 (95% UI: 0.64–1.12) in 2021. DALYs in China increased from 227,509 (95% UI: 174,534–293,034) in 1990 to 477,847 (95% UI: 352,518–637,755) in 2021, reflecting a 110.03% rise in LCAL-related DALYs over the past 32 years. The trend of ASDR for LCAL in China showed a downward trajectory from 1990 to 2021; however, this change was not statistically significant (AAPC: −0.25%, 95% CI: −0.67%, 0.17%, $p = 0.247$) (Fig. 1H), with ASDRs per 100,000 population being 24.26 (95% UI: 18.72–31.11) in 1990 and 22.01 (95% UI: 16.30–29.15) in 2021. According to the GBD study criteria, China falls within the high-middle SDI region. In 2021, the number of liver cancer-related deaths (18,317; 95% UI: 13,653–24,252) in China exceeded that in other countries and territories (Fig. 2B). LCAL-related deaths increased by varying percentages across different SDI regions from 1990 to 2021, with notable increases in DALYs as well. The trends of ASMRs and ASDRs from 1990 to 2021 in different SDI regions exhibited various patterns, with some regions (i.e., high, middle, and low-middle) showing upward trends and others (i.e., high-middle and low) displaying downward trends. These results had varying levels of statistical significance (Table 2).

Burden of LCHB and LCAL across sex and age

To provide a clearer understanding of the disease burden associated with LCHB and LCAL, subgroup analyses were conducted to examine the burden across sex and age. Globally, both the number of deaths and DALYs for LCHB increased for females and males from 1990 to 2021 (Table 1); however, during the same period, the ASMR and ASDR per 100,000 population decreased. Notably, these measures were consistently higher for males than for females and were similarly observed in China. In 1990, the age groups '40–44 years (301,327, 95% UI: 240,691–370,832),' '45–49 years (292,217, 95% UI: 228,048–358,513),' and '50–54 years (289,389, 95% UI: 229,238–356,177)' showed the highest DALYs for LCHB in China, whereas globally, the corresponding age groups were '50–54 years (509,745, 95% UI: 422,188–607,747)', '55–59 years (494,279, 95% UI: 400,944–599,170)', and '45–49 years (461,271, 95% UI: 386,119–550,406)'. By 2021, the age groups with the highest DALYs remained consistent in both China and globally, specifically for the age groups '50–54,' '55–59,' and '45–49' years (Fig. 3A).

The global number of deaths, DALYs, and ASMR per 100,000 population showed significant increases for both females and males from 1990 to 2021 regarding LCAL (Table 2). Additionally, the ASDR per 100,000 population increased only for males over this period, while it remained relatively stable for females. These measures consistently showed higher values for males than for females, similar to the trends noted for LCHB. In China, the number of deaths and DALYs increased for both sexes from 1990 to 2021, with a significant decrease in ASDR per 100,000 population for females. Analysis of the different age subgroups in 1990 and 2021 revealed '55–59,' '60–64,' and '65–69' years as the top three age groups with the highest DALYs in both China and globally. However, the specific age group with the highest DALYs did not always remain the same (Fig. 3B).

Age-period-cohort analysis of LCHB and LCAL burden

The results of the age-period-cohort analysis on the mortality rate of LCHB at the global scale are illustrated in Figure

Table 1. LCHB burden in 1990 and 2021, and the temporal trend from 1990 to 2021

	1990 (95% UI)				2021 (95% UI)				1990–2021 (95% CI)	
	Mortality	ASMR /10^5	DALYs	ASDR /10^5	Mortality	ASMR /10^5	DALYs	ASDR /10^5	AAPC of ASMR, P	AAPC of ASDR, P
Global										
Both	106,514 (91,940, 124,291)	2.50 (2.15, 2.92)	3,748,179 (3,255,634, 4,362,511)	84.16 (73.10, 97.96)	181,194 (148,896, 221,685)	2.09 (1.72, 2.55)	5,668,199 (4,706,886, 6,885,071)	65.36 (54.43, 79.35)	−0.58 (−0.81, −0.36), <0.001	−0.79 (−1.01, −0.56), <0.001
Female	20,474 (16,329, 25,357)	0.93 (0.74, 1.16)	676,140 (551,000, 817,561)	29.78 (24.25, 36.3)	34,688 (27,676, 42,913)	0.76 (0.61, 0.94)	999,293 (814,569, 1,216,039)	22.5 (18.37, 27.27)	−0.63 (−0.82, −0.44), <0.001	−0.90 (−1.11, −0.69), <0.001
Male	86,040 (73,638, 100,603)	4.20 (3.59, 4.92)	3,072,039 (2,626,206, 3,564,854)	140.16 (119.77, 162.77)	146,506 (118,397, 182,374)	3.54 (2.87, 4.41)	4,668,906 (3,794,780, 5,803,284)	110.11 (89.43, 136.48)	−0.55 (−0.79, −0.32), <0.001	−0.75 (−1.00, −0.49), <0.001
China										
Both	61,415 (50,743, 73,122)	6.53 (5.42, 7.76)	2,236,077 (1,842,616, 2,663,358)	220.05 (181.34, 260.91)	100,194 (77,721, 129,138)	4.83 (3.76, 6.19)	3,148,553 (2,442,865, 4,109,014)	155.81 (121.32, 201.99)	−0.93 (−1.35, −0.51), <0.001	−1.07 (−1.52, −0.62), <0.001
Female	9,890 (7,690, 12,251)	2.18 (1.70, 2.70)	335,318 (264,347, 410,310)	68.37 (54.05, 84.20)	15,129 (11,159, 19,856)	1.40 (1.04, 1.84)	415,170 (306,814, 554,410)	39.71 (29.57, 52.76)	−1.43 (−1.79, −1.06), <0.001	−1.68 (−2.04, −1.32), <0.001
Male	51,525 (41,305, 62,899)	10.96 (8.85, 13.33)	1,900,759 (1,528,585, 2,319,159)	365.38 (293.80, 446.15)	85,065 (63,905, 114,760)	8.48 (6.42, 11.29)	2,733,383 (2,046,835, 3,699,193)	271.87 (204.97, 364.75)	−0.79 (−1.24, −0.35), <0.001	−0.91 (−1.37, −0.44), <0.001
SDI regions										
High	15,699 (13,141, 18,507)	1.50 (1.26, 1.77)	499,137 (424,579, 590,146)	49.07 (41.64, 57.82)	22,541 (18,388, 27,202)	1.17 (0.97, 1.40)	577,543 (479,217, 691,358)	33.50 (28.16, 39.80)	−0.79 (−1.08, −0.51), <0.001	−1.18 (−1.50, −0.87), <0.001
High-middle	29,654 (24,699, 35,265)	2.86 (2.39, 3.41)	1,055,382 (880,686, 1,247,422)	100.12 (83.52, 118.58)	47,895 (37,909, 60,440)	2.50 (1.99, 3.16)	1,487,086 (1,177,832, 1,882,872)	80.79 (64.35, 102.24)	−0.39 (−0.82, 0.05), 0.081	−0.66 (−1.00, −0.32), <0.001
Middle	45,528 (38,954, 52,953)	3.86 (3.31, 4.50)	1,647,718 (1,400,349, 1,931,330)	127.53 (108.54, 149.01)	81,087 (64,898, 101,641)	2.92 (2.35, 3.64)	2,582,133 (2,080,861, 3,255,381)	90.66 (73.31, 114.04)	−0.89 (−1.19, −0.58), <0.001	−1.07 (−1.35, −0.79), <0.001
Low-middle	8,694 (6,805, 11,281)	1.27 (0.99, 1.64)	307,387 (241,167, 392,407)	40.35 (31.69, 51.90)	18,249 (14,603, 23,064)	1.18 (0.95, 1.49)	615,623 (494,362, 769,789)	36.97 (29.77, 46.50)	−0.25 (−0.38, −0.13), <0.001	−0.29 (−0.44, −0.14), <0.001
Low	6,894 (4,538, 9,894)	2.79 (1.84, 4.00)	237,066 (157,821, 332,320)	84.29 (55.50, 120.55)	11,352 (8,479, 14,986)	1.97 (1.47, 2.62)	403,657 (304,906, 539,507)	60.42 (45.26, 80.28)	−1.12 (−1.28, −0.96), <0.001	−1.07 (−1.22, −0.92), <0.001

ASMR, age-standardized mortality rate; DALYs, disability-adjusted life years; ASDR, age-standardized DALYs rate; AAPC, average annual percentage change; UI, uncertainty interval; CI, confidence interval; SDI, sociodemographic index.
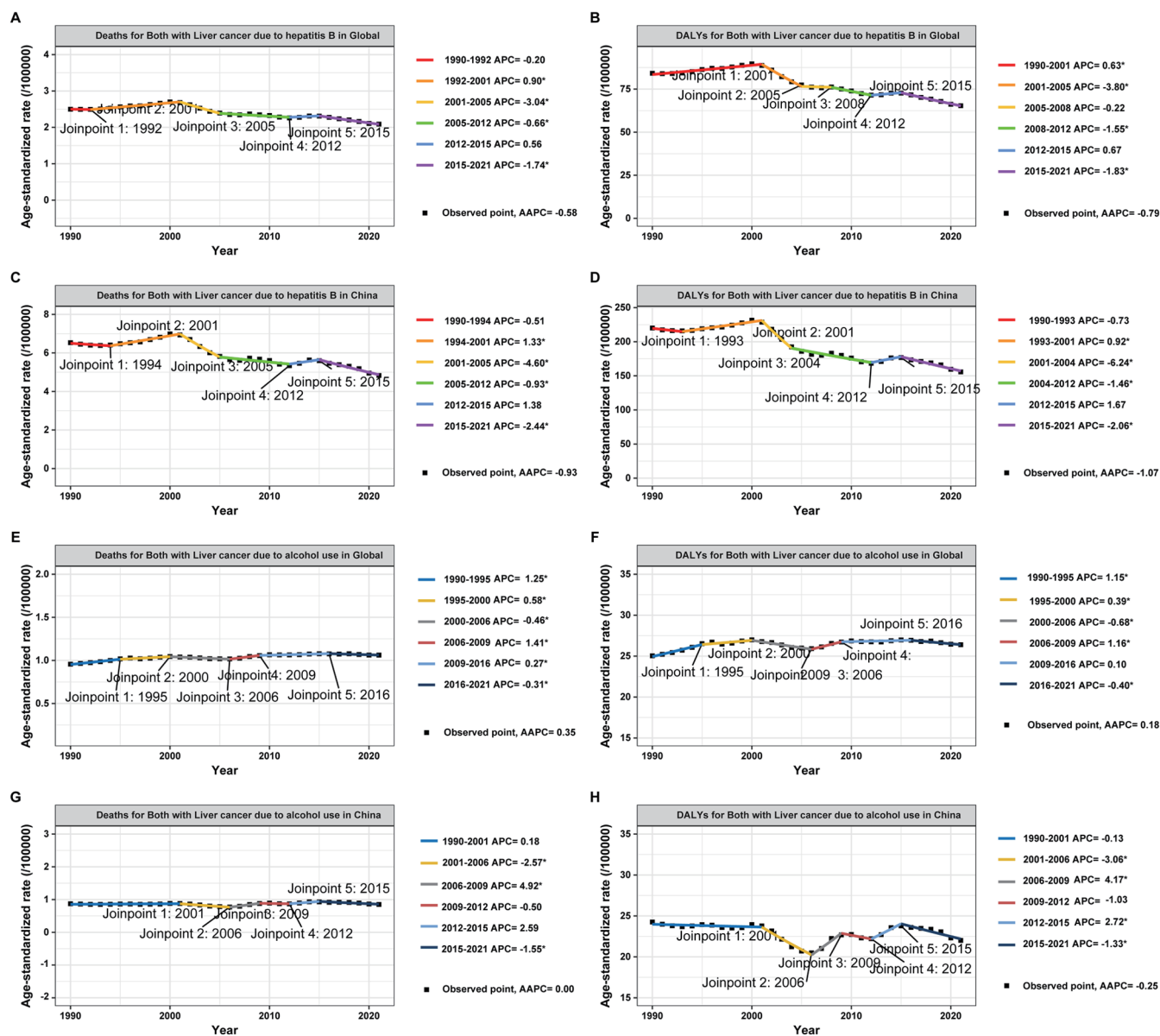
Fig. 1. Joinpoint regression of ASMR and ASDR for LCHB and LCAL. (A, B) Deaths and disability-adjusted life years for both with LCHB in global, respectively, (C, D) Deaths and disability-adjusted life years for both with LCHB in China, respectively, (E, F) Deaths and disability-adjusted life years for both with LCAL in global, respectively, (G, H) Deaths and disability-adjusted life years for both with LCAL in China, respectively. *$p < 0.05$. ASMR, Age-standardized mortality rate; ASDR, Age-standardized disability-adjusted life years rate; LCHB, Liver cancer due to hepatitis B; LCAL, Liver cancer due to alcohol use; APC, Annual percentage change; AAPC, Average annual percentage change.

4A–D. The net drift, representing the APC of the expected age-adjusted rates from 1992 to 2021, was calculated to be −0.83% (95% CI: −0.97%, −0.69%, $p < 0.001$) for both sexes combined. It was −0.84% (95% CI: −1.01%, −0.67%, $p < 0.001$) for males and −0.93% (95% CI: −1.03%, −0.82%, $p < 0.001$) for females. These findings suggest a favorable decreasing trend in the mortality rate associated with LCHB across all sexes. The local drift illustrates the APC in the mortality rate linked to LCHB across various age groups from 10–14 years to 95+ years (Fig. 4A). The patterns in the local drift curves are parallel, demonstrating a consistent upward trend with age across all sex cohorts.

The longitudinal age curve displays the age-specific rates

in the reference cohort, considering period deviations to represent age effects (Fig. 4B). Within the same birth cohort, the mortality rate linked to LCHB increased with age, particularly from 30 years of age, with the female group and both sexes reaching a peak at 80–84 years, while the male group peaked at 85–89 years. Additionally, the RR of the cohort denotes the ratio of the age-specific rate in a specific birth cohort to that in the reference cohort.[15] In successive birth cohorts, after adjustments for age and period effects, the patterns of cohort RRs for the mortality rate in all sex groups were similar, with RRs increasing and peaking for those born during 1927–1936, before subsequently fluctuating downward (Fig. 4C). The period RR signifies the ratio of
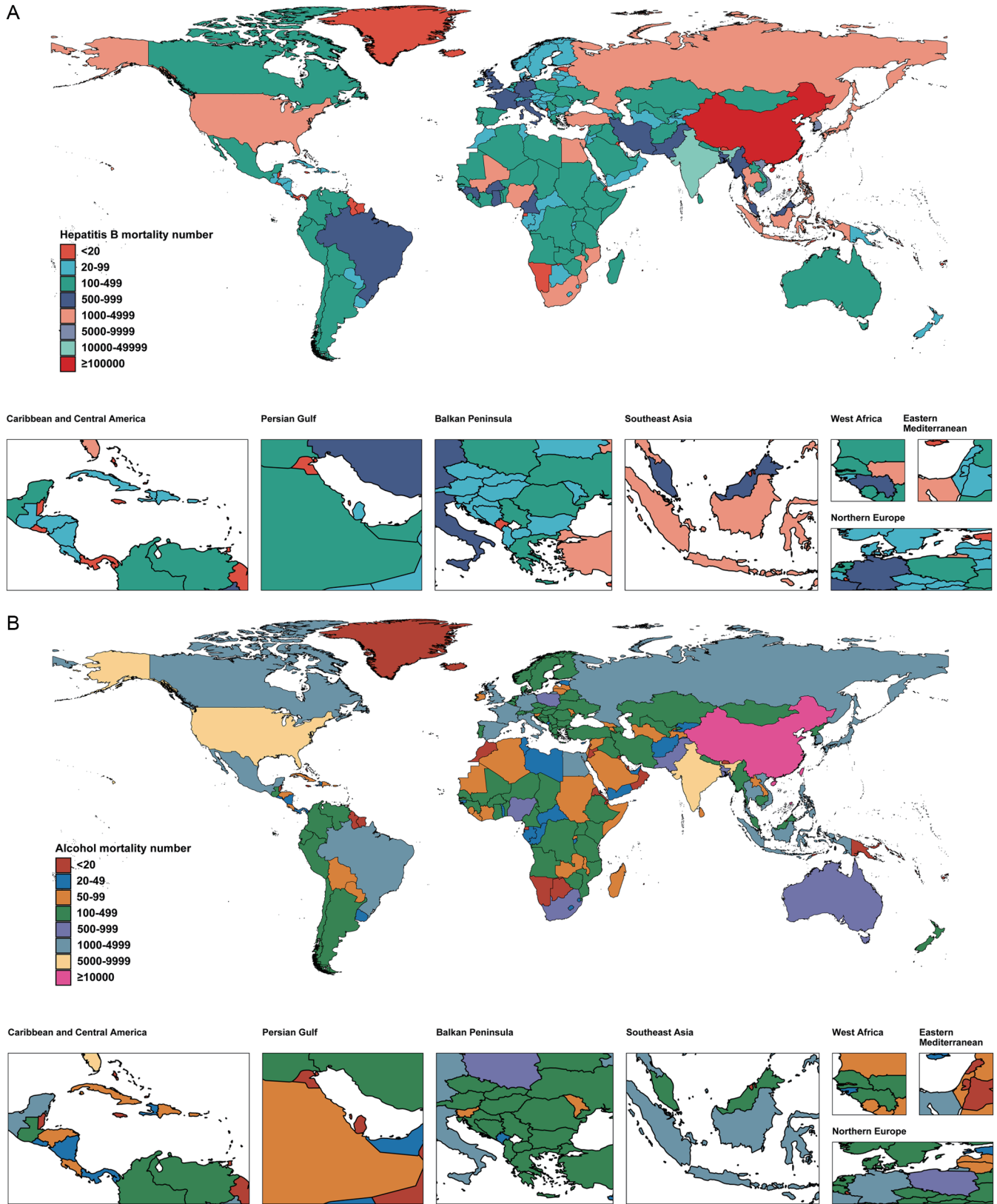
A

B

Fig. 2. Mortality number of LCHB and LCAL in 2021. (A) Mortality number of LCHB, (B) Mortality number of LCAL. LCHB, Liver cancer due to hepatitis B; LCAL, Liver cancer due to alcohol use.

Table 2. LCAL burden in 1990 and 2021, and the temporal trend from 1990 to 2021

	1990 (95% UI)				2021 (95% UI)				1990–2021 (95% CI)	
	Mortality	ASMR /10^5	DALYs	ASDR /10^5	Mortality	ASMR /10^5	DALYs	ASDR /10^5	AAPC of ASMR, P	AAPC of ASDR, P
Global										
Both	38,172 (31,170, 46,200)	0.96 (0.78, 1.15)	1042,116 (852,871, 1280,544)	25.03 (20.59, 30.5)	92,228 (75,053, 112,160)	1.06 (0.86, 1.29)	2316,027 (1887,013, 2845,789)	26.39 (21.53, 32.28)	0.35 (0.22, 0.49), <0.001	0.18 (0.05, 0.32), 0.008
Female	9,151 (7,228, 11,508)	0.43 (0.34, 0.54)	237,030 (187,915, 295,375)	10.89 (8.62, 13.62)	20,960 (16,643, 25,768)	0.45 (0.36, 0.56)	499,661 (398,674, 613,743)	10.90 (8.73, 13.38)	0.16 (0.00, 0.33), 0.047	0.00 (−0.24, 0.23), 0.971
Male	29,021 (23,918, 35,445)	1.59 (1.32, 1.93)	805,086 (661,942, 991,046)	40.82 (33.87, 49.76)	71,268 (58,195, 86,613)	1.77 (1.45, 2.13)	1816,366 (1477,467, 2246,606)	43.36 (35.34, 53.29)	0.36 (0.24, 0.47), <0.001	0.21 (0.08, 0.34), 0.001
China										
Both	7,575 (5,858, 9,677)	0.87 (0.69, 1.10)	227,509 (174,534, 293,034)	24.26 (18.72, 31.11)	18,317 (13,653, 24,252)	0.85 (0.64, 1.12)	477,847 (352,518, 637,755)	22.01 (16.30, 29.15)	0.00 (−0.51, 0.52), 0.987	−0.25 (−0.67, 0.17), 0.247
Female	2,659 (1,976, 3,433)	0.61 (0.46, 0.78)	75,746 (55,929, 98,525)	16.45 (12.21, 21.46)	6,119 (4,472, 8,144)	0.54 (0.40, 0.73)	149,332 (107,233, 198,685)	13.34 (9.60, 17.61)	−0.33 (−0.80, 0.15), 0.177	−0.65 (−1.09, −0.19), 0.005
Male	4,916 (3,680, 6,553)	1.15 (0.87, 1.49)	151,763 (113,195, 203,754)	32.04 (24.17, 42.63)	12,198 (8,489, 17,015)	1.19 (0.85, 1.62)	328,515 (220,222, 469,326)	30.96 (21.08, 43.77)	0.18 (−0.41, 0.77), 0.560	−0.05 (−0.45, 0.34), 0.785
SDI regions										
High	11,990 (10,070, 14,060)	1.08 (0.91, 1.27)	301,470 (252,551, 352,927)	28.03 (23.37, 33.16)	28,568 (23,765, 33,859)	1.36 (1.13, 1.61)	629,166 (525,978, 743,027)	32.31 (27.07, 38.00)	0.74 (0.53, 0.95), <0.001	0.45 (0.22, 0.67), <0.001
High-middle	9,802 (8,131, 11,665)	0.97 (0.81, 1.15)	266,746 (221,534, 322,391)	25.72 (21.45, 31.08)	18,544 (15,108, 22,320)	0.92 (0.76, 1.11)	460,739 (369,141, 560,832)	23.22 (18.73, 28.25)	−0.14 (−0.56, 0.28), 0.511	−0.32 (−0.76, 0.13), 0.168
Middle	9,708 (7,874, 12,146)	0.93 (0.75, 1.16)	282,796 (225,932, 356,838)	24.72 (20.03, 31.23)	28,334 (22,395, 35,632)	1.04 (0.83, 1.29)	757,205 (596,635, 964,476)	26.71 (21.14, 33.67)	0.39 (0.26, 0.52), <0.001	0.26 (0.14, 0.38), <0.001
Low-middle	3,960 (3,054, 5,162)	0.65 (0.5, 0.85)	113,838 (86,820, 151,225)	17.04 (13.09, 22.40)	11,579 (9,277, 14,972)	0.80 (0.64, 1.02)	320,756 (254,346, 411,303)	20.81 (16.58, 26.83)	0.65 (0.49, 0.81), <0.001	0.63 (0.48, 0.78), <0.001
Low	2,664 (1,729, 3,886)	1.19 (0.78, 1.76)	76,038 (48,926, 109,911)	30.72 (19.92, 44.69)	5,117 (3,703, 7,020)	1.02 (0.74, 1.40)	146,071 (104,518, 203,238)	26.02 (18.66, 35.91)	−0.53 (−0.68, −0.37), <0.001	−0.56 (−0.69, −0.43), <0.001

ASMR, age-standardized mortality rate; DALYs, disability-adjusted life years; ASDR, age-standardized DALYs rate; AAPC, average annual percentage change; UI, uncertainty interval; CI, confidence interval; SDI, sociodemographic index.
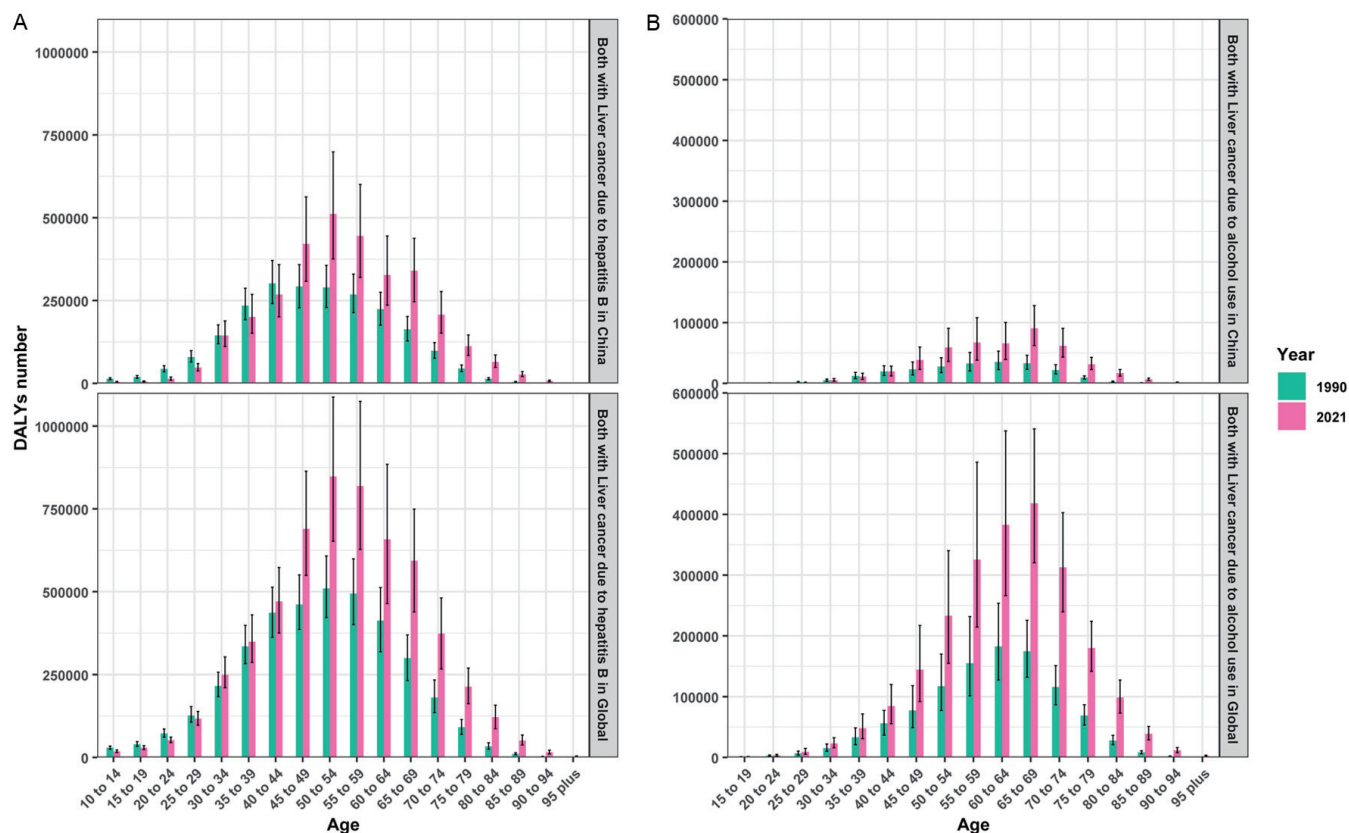
Fig. 3. Age differences in DALYs for LCHB and LCAL. (A) Both with LCHB in China (top) and global (bottom), (B) Both with LCAL in China (top) and global (bottom). DALYs, Disability-adjusted life years; LCHB, Liver cancer due to hepatitis B; LCAL, Liver cancer due to alcohol use.

the age-specific rate in a specific period to that in the reference period.[15] After adjustments for age and birth cohort effects, the period RRs for males and both sexes increased initially and then decreased gradually, with an identical peak in 1997–2001 (1.10, 95% CI: 1.07, 1.13). In contrast, for the female group, there was a gradual reduction in the period RR over the study duration (Fig. 4D).

Results from the age-period-cohort analysis on the mortality rate of LCAL at the global scale are depicted in Figure 4E–H. The net drift was estimated at 0.06% (95% CI: −0.04%, 0.16%) for both sexes combined, with 0.07% (95% CI: −0.05%, 0.19%) for the male group and −0.09% (95% CI: −0.27%, 0.09%) for the female group. These data indicate that changes observed in the mortality rate of LCAL across all sex groups were not pronounced (Wald test, *p* > 0.05 for all net drifts, Supplementary File 2). Moreover, the local drift illustrates the APC in the mortality rate of LCAL across various age groups from 15–19 years to 95+ years (Fig. 4E). Similarly, trends in the local drift of the mortality rate associated with LCAL show a general fluctuating increase with age across all sex groups.

Within the same birth cohort, the mortality rate of LCAL increased with age, becoming evident from 45 years of age, with all sex groups peaking at 80–84 years but with different values (Fig. 4F). In successive birth cohorts, after adjusting for age and period effects, the trends of cohort RRs for the mortality rate in all sex groups were analogous, with RRs showing fluctuations, increasing, and peaking for those born in 1927–1936 for both sexes combined, in 1947–1956 for the female group, and in 1952–1961 for the male group before

declining (Fig. 4G). After adjusting for age and birth cohort effects, the period RRs for the male group exhibited an initial increase, followed by a decrease, and then an increase again; for the female and both sex groups, there was an initial decrease followed by an increase in the RR over the course of the study (Fig. 4H).

Decomposition analysis of LCHB and LCAL burden

Decomposition analysis was conducted to determine the influence of aging, population growth, and epidemiological shifts on raw mortality numbers and DALYs related to LCHB and LCAL from 1990 to 2021. The results are presented in Figure 5A–D and Supplementary File 3. A pronounced increase in mortality numbers and DALYs associated with LCHB was observed globally, in China, and in the middle SDI regions across all areas (Fig. 5A, B). Epidemiological shifts refer to changes in age- and population-adjusted morbidity and mortality rates of liver cancer. Importantly, these transitions have played a major role in mitigating the increase in mortality rates and DALYs related to LCHB in all areas. Globally, population growth emerged as the most significant positive factor driving the increase in deaths (86.89%) and DALYs (112.25%), followed by aging at 50.39% and 52.20%, respectively. Conversely, in China, aging had the most substantial positive impact on the escalation of mortality (112.78%) and the increase in DALYs (127.58%), surpassing population growth at 55.05% and 78.55%, respectively. Furthermore, population growth had the most significant positive influence on the increase in deaths and DALYs due to LCHB in the low, low-middle, and middle SDI regions, with the greatest im-
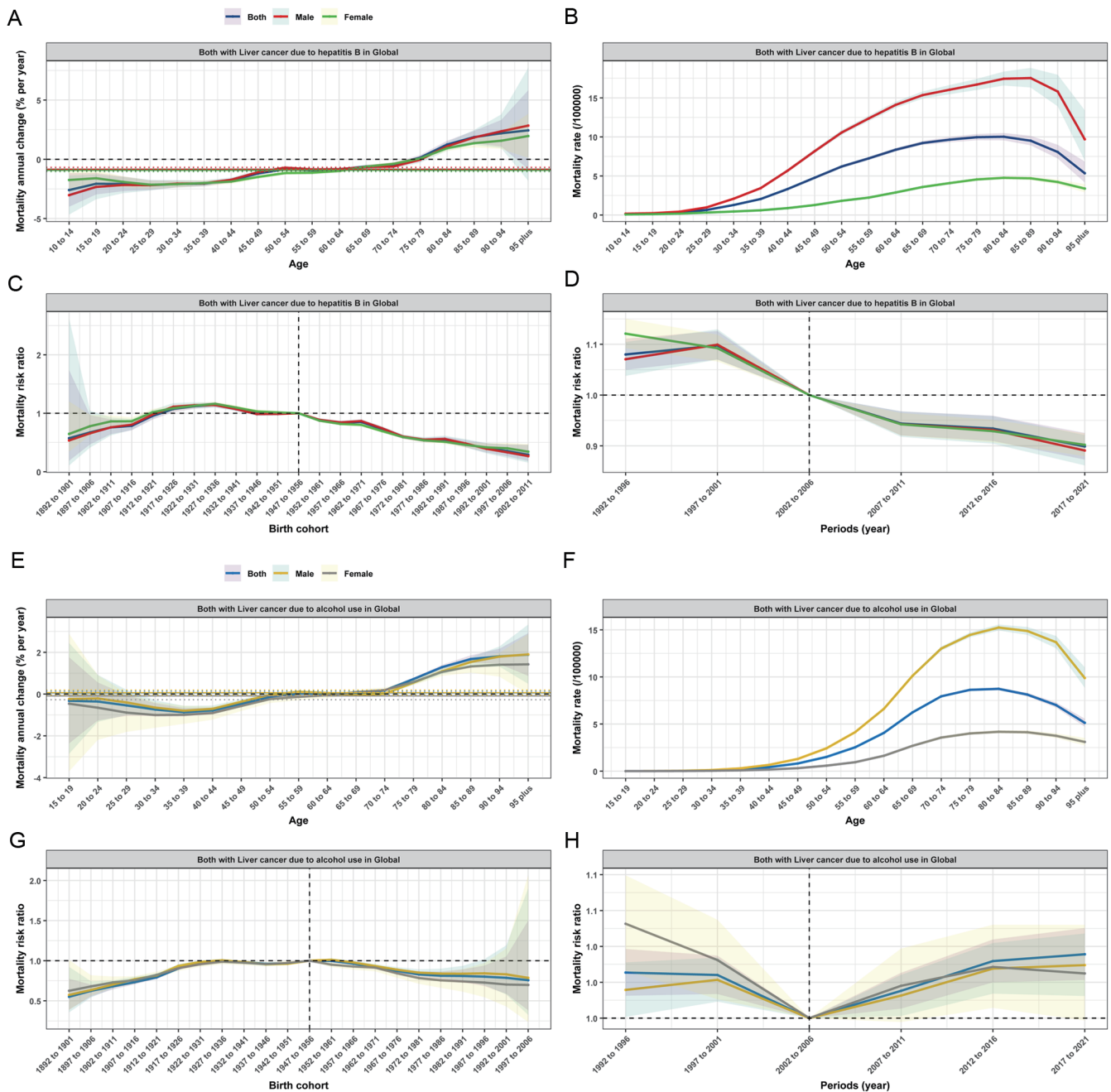
Fig. 4. Age-period-cohort analysis of LCHB and LCAL mortality. (A–D) Local drift, age effect, cohort effect, and period effect of LCHB mortality risk in global, respectively, (E–F) Local drift, age effect, cohort effect, and period effect of LCAL mortality risk in global, respectively. LCHB, Liver cancer due to hepatitis B; LCAL, Liver cancer due to alcohol use.

pact on increased DALYs in high SDI regions. In contrast, aging had the most substantial positive effect on the increase in deaths and DALYs associated with LCHB in the high-middle region, while predominantly contributing to the surge in deaths in the high SDI regions.

Regarding the impact of aging, population growth, and epidemiological changes on mortality figures and DALYs for LCAL, a notable increase in mortality numbers and DALYs related to LCAL was observed globally and in the middle and high SDI regions (Fig. 5C, D). In contrast to the impact on

LCHB, the effect of epidemiological changes on LCAL varied across regions, with some showing a positive contribution and others demonstrating a negative influence. Nonetheless, similar to LCHB, population growth was identified as the most substantial positive factor driving the increase in deaths (55.23%) and DALYs (61.11%) from LCAL globally, followed by aging at 34.00% and 32.95%, respectively. In China, aging had the most significant positive effect on the increase in mortality (70.78%) and DALYs (73.40%), surpassing population growth at 34.88% and 41.39%, respec-
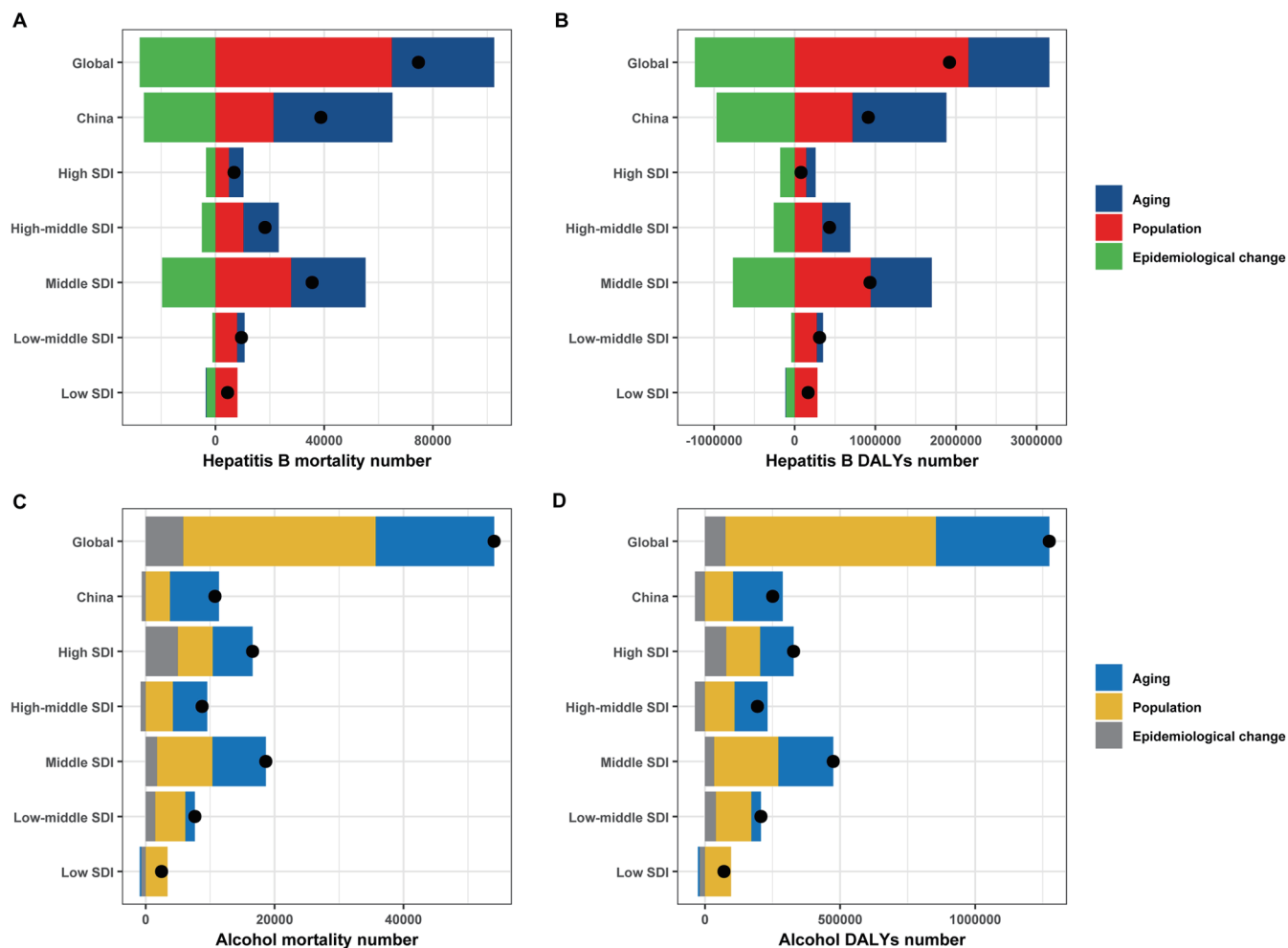
Fig. 5. Decomposition analysis of mortality and DALYs for LCHB and LCAL. (A, B) Mortality and DALYs number of LCHB, respectively, (C, D) Mortality and DALYs number of LCAL, respectively. DALYs, Disability-adjusted life years; LCHB, Liver cancer due to hepatitis B; LCAL, Liver cancer due to alcohol use; SDI, sociodemographic index.

tively. Additionally, population growth had the most substantial positive impact on the increase in deaths and DALYs due to LCAL in low, low-middle, and middle SDI regions. In high SDI regions, aging had the most significant positive impact on the increase in deaths, while population growth had the greatest positive influence on the increase in DALYs. Aging played a prominent role in the surge in deaths and DALYs in the low-middle SDI regions.

Health inequality analysis and prediction analysis on LCHB and LCAL burden

To assess disparities in health equity among countries and territories, the slope index and concentration index were used to analyze the distribution of LCHB and LCAL burden in 204 countries and territories from 1990 to 2021. Significant and varied absolute and relative inequalities related to SDI were noted. The slope index of the rate of DALYs per 100,000 population due to LCHB between the countries and territories with the highest and lowest SDIs increased from −22.09 (95% CI: −33.87, −10.31) in 1990 to −12.71 (95% CI: −25.28, −0.15) in 2021 (Fig. 6A). Countries and territories with lower SDIs were found to bear a disproportionately heavier burden of LCHB. A reduction in these absolute values

indicated a decline in health disparities over time, while the concentration index increased from 0.03 (95% CI: −0.06, 0.13) in 1990 to 0.22 (95% CI: 0.13, 0.30) in 2021 (Fig. 6B).

Furthermore, the difference in the rate of DALYs per 100,000 population attributed to LCAL between countries and territories with the highest and lowest SDIs increased from 10.97 (95% CI: 4.46, 17.49) in 1990 to 37.75 (95% CI: 28.47, 47.04) in 2021 (Fig. 6C). Countries and territories with higher SDIs were found to bear a disproportionately higher burden of LCAL. The increase in these absolute values indicated an increase in health disparities over time, with the concentration index rising from 0.24 (95% CI: 0.18, 0.30) in 1990 to 0.27 (95% CI: 0.21, 0.33) in 2021 (Fig. 6D).

Additionally, the projected mortality numbers for LCHB and LCAL were forecasted from 2022 to 2030 in China and globally using the integrated nested Laplace approximation framework and the Bayesian age-period-cohort model (Fig. 7A, B). Overall, the mortality numbers linked to liver cancer due to LCHB and LCAL are anticipated to increase notably among males and both sexes in China and globally. Conversely, the mortality numbers for LCHB and LCAL among females are projected to remain relatively stable in the forthcoming years.
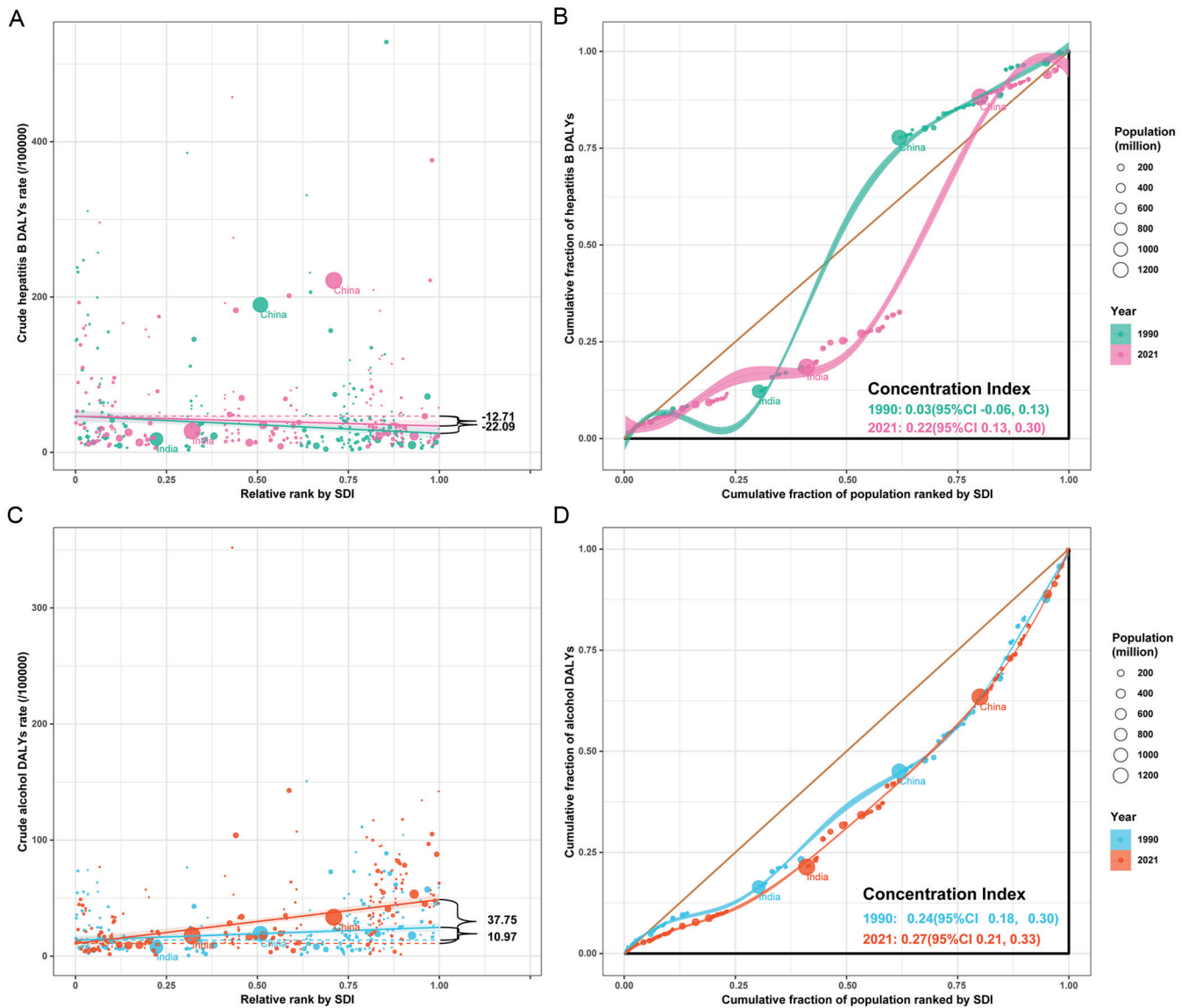
Fig. 6. Health inequality analysis of DALYs for LCHB and LCAL. (A, B) slope index and concentration index of DALYs rate for LCHB, respectively, (C, D) slope index and concentration index of DALYs rate for LCAL, respectively. DALYs, Disability-adjusted life years; LCHB, Liver cancer due to hepatitis B; LCAL, Liver cancer due to alcohol use; SDI, sociodemographic index.

Discussion

This in-depth analysis of the mortality and DALY burden associated with LCHB and LCAL in China, globally, and across five SDI regions utilized data from the GBD 2021 database. The findings revealed a persistently substantial burden related to LCHB and LCAL, with deaths linked to these conditions projected to continue increasing globally and in China in the coming years.

Hepatitis B remains the primary cause of liver cancer worldwide, with hepatitis B virus (HBV) infection and chronic hepatitis B playing critical roles in the development of liver cancer, particularly in China.[2,17] Such trends persist despite global efforts by the World Health Organization (WHO) and various countries to combat HBV infection and associated conditions. For instance, the WHO's 2016 global elimination strategy aimed to eradicate hepatitis B as a public health threat by 2030,[18] while an early initiative in China was the

formal integration of hepatitis B vaccination into its immunization program in 1992.[19] Our study shows a decreasing trend in ASMR and ASDR of LCHB globally, in China, and across various SDI regions compared with 1990. However, there was a notable increase in the absolute number of deaths and DALYs associated with LCHB in 2021, with China recording the highest number of LCHB-related deaths that year. These results highlight the urgency for intensified efforts to alleviate the mortality and DALY burden of LCHB. Sex disparities were evident, with males experiencing a significantly higher disease burden than females. This finding may be influenced by societal contexts, lifestyles, physiological differences,[20] and hormonal signaling pathways, all contributing to sex disparities in HBV infections and LCHB development, as reported in several studies.[21,22]

Our further analysis using an age-period-cohort framework indicated a general increase in global LCHB death rates
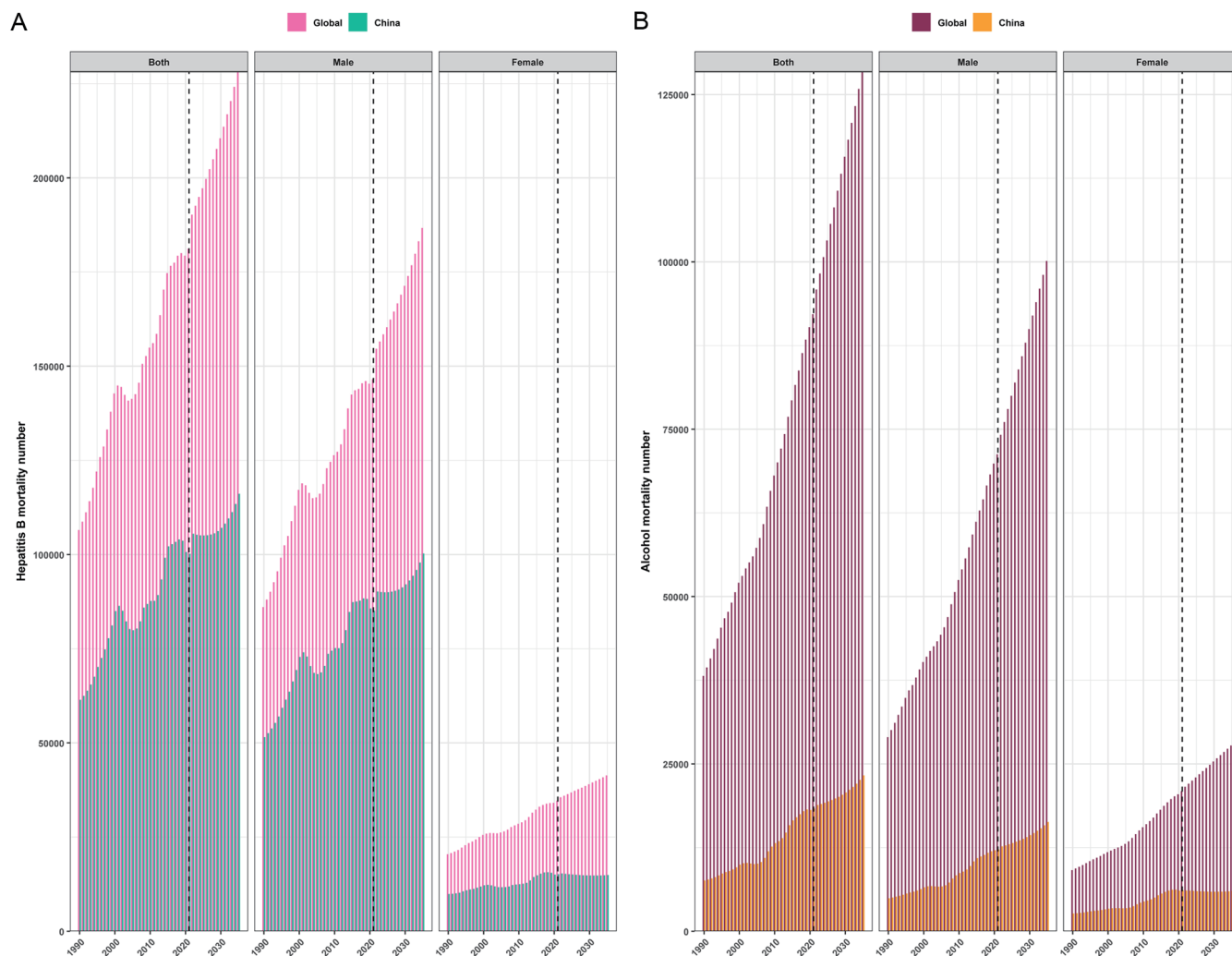
Fig. 7. Prediction on mortality number of LCHB and LCAL. (A) Predicted mortality number of LCHB, (B) Predicted mortality number of LCAL. LCHB, Liver cancer due to hepatitis B; LCAL, Liver cancer due to alcohol use.

with age, with a concentration of DALYs among the 40–70 age group, underscoring the need for focused public health attention and prevention strategies for these age cohorts. Younger cohorts and more recent periods showed a reduced risk of LCHB mortality, potentially reflecting the effectiveness of diverse prevention and control measures implemented in recent decades, including advancements in HBV diagnosis and treatment technologies and successful health policies.[23,24] Encouraging evidence related to a decline in HBV infection rates among the Chinese population was presented in a recent meta-analysis, showing a reduction in HBsAg seroprevalence in the general population from 9.6% in 1973–1984 to 3.0% in 2021.[25] Furthermore, in 2022, the WHO introduced the "Global health sector strategies on HIV, viral hepatitis, and sexually transmitted infections for the period 2022–2030",[26] and the effective implementation of these strategies is expected to play a crucial role in reducing the burden of death and DALYs due to LCHB in the coming years.

Alcohol, a common component in daily routines, is associated with various liver illnesses ranging from steatosis to liver cancer.[27,28] However, the direct mechanisms through which ethanol and its metabolites mediate carcinogenic ef-

fects on LCAL remain uncertain.[28] Per capita alcohol consumption among adults globally increased from 5.9 L in 1990 to 6.5 L in 2017, with a projected rise to 7.6 L by 2030.[29] Notably, China has experienced a sharper spike in alcohol consumption compared with other global regions, increasing from 0.4 L in 1952 to 4.9 L in 2009. The annual average alcohol intake among individuals aged 15 years and older in China continues to rise.[29,30] These trends may partially explain the significant increase in absolute mortality and DALYs related to LCAL observed in China, globally, and in the five SDI regions in 2021 compared with 1990. This shift highlights a transition in the disease burden from communicable to noncommunicable diseases. Furthermore, the study uncovered a significant male predilection for LCAL burden, likely due to higher alcohol consumption among men. For example, 55.6% of males and 15.0% of females consume alcoholic beverages in China,[29,30] emphasizing the need for global initiatives to regulate alcohol consumption. Strategies include promoting health awareness through mass and social media, introducing school-based campaigns, restricting alcohol promotion, increasing taxes on alcoholic beverages, and raising the legal drinking age.[3,27]

The age-period-cohort analysis of LCAL mortality rates demonstrated a general increase with advancing age, with the concentration of DALYs among the 50–75 age group potentially influenced by age-related effects on alcohol metabolism.[31] Additionally, there has been a recent increase in mortality rates due to LCAL, likely influenced by rising societal stress and shifts in lifestyle choices that encourage higher alcohol intake.[32,33] However, notable changes in cohort effects for LCAL have not been prominent. In 2016, the Chinese government introduced the "Healthy China 2030" blueprint, which included explicit measures to curb alcohol consumption and smoking (another liver cancer risk factor).[2,34] A recent large-scale study also found that years of alcohol consumption, age, diabetes mellitus, HBV infection, liver cirrhosis, and male sex were independently associated with an elevated liver cancer risk in patients with alcohol-related liver disease.[35] Therefore, effectively controlling liver cancer may necessitate comprehensive prevention and control measures specifically targeting a healthier lifestyle. Moreover, the WHO recently introduced the "Global alcohol action plan 2022–2030",[36] which aims to reduce the harmful effects of alcohol use through evidence-based strategies and is expected to positively impact the reduction in LCAL burden.

In addition, decomposition analysis revealed that among three factors—aging population, population growth, and epidemiological changes—population growth had the most significant impact on the changing burden of LCHB and LCAL globally, whereas population aging was the primary factor altering the liver cancer burden in China. Notably, China has emerged as a country with the largest population of individuals aged 60 years or older.[37] This study also noted a higher LCHB burden in countries with lower SDI levels, likely due to constrained medical resources and inadequate healthcare capabilities.[38,39] Conversely, a higher LCAL burden was observed in countries with higher SDI levels, likely due to socioeconomic factors that facilitated easier access to alcohol and higher alcohol consumption prevalence.[29] These findings emphasize the need for tailored prevention and control strategies targeted to specific socioeconomic strata to mitigate liver cancer–related deaths.

Our study has several strengths. To the best of our knowledge, this is the first comprehensive analysis investigating the epidemiological trends of LCHB and LCAL globally, in China, and across five SDI regions from 1990 to 2021 using the GBD 2021 database. In addition to a descriptive analysis of the disease burden, additional analyses—including age-period-cohort analysis, decomposition analysis, and health inequality assessment—were performed, providing a novel perspective on the burden of these conditions. Overall, our findings can serve as a basis for other GBD-based investigations. Furthermore, our study evaluated not only mortality but also DALYs, offering a thorough understanding of the disease burden by capturing the impacts of both death and disability.

However, our study also has some limitations similar to those of its counterparts. The disease burden data reported in GBD 2021 are based on mathematical modeling estimates derived from various epidemiological sources, which may lead to deviations from actual figures.[40] Limited resources in underfinanced health systems in some regions may constrain diagnosis, treatment, and investigation capacities, impacting data accuracy.[3,9] However, the GBD collaborator network has made several efforts to address issues such as incompleteness, underreporting, and misclassification to improve data quality and comparability.[7,16] Additionally, UIs are provided for each dataset to indicate inherent data uncertainty in such data analyses.[7] Focusing on national-level data could intro-duce ecological fallacies in the findings.[8] Furthermore, using five-year intervals for age and period in the analysis lacks finer granularity. Therefore, future research should prioritize real population surveys, particularly at smaller geographic levels (e.g., provinces, cities), and provide more refined temporal resolutions.

Conclusions

Despite significant past efforts, the burden of death and DALYs from LCHB and LCAL remains substantially high both globally and in China. Prompt action on a global scale that is data-driven and evidence-based, along with investments through resource allocations, is imperative to implement more effective primary and secondary prevention measures (e.g., ultrasound screening and surveillance) and control strategies. These approaches should encompass public health policies and innovative treatments, such as immunotherapies and digital therapies, to address the rising disease burden associated with LCHB and LCAL.

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Investigation (all authors), writing–original draft (XD, HL, CL), methodology (XD, HL, CL), validation (XD), data curation (XD, HL, LK, CL), funding acquisition (HL), supervision (HL, CL), visualization (YZ, HW, CL), writing–review and editing (YZ, HW, LK, ZW, AFM, YX, ZQ), conceptualization (CL). All authors have approved the final version and publication of the manuscript.

Ethical statement

This study utilized publicly available population-level data and is therefore exempt from requiring ethical approval by an Ethics Committee or Institutional Review Board. The written informed consent is waived.

Data sharing statement

In addition to being publicly available through the GBD 2021 project, the data supporting the findings of this study are available upon request from the corresponding authors.

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