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The burden of liver cirrhosis and underlying etiologies: results from the Global Burden of Disease Study 2019

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Abstract

Background: Liver cirrhosis is a major health concern. Herein, we aimed to estimate the incidence, prevalence, and mortality of liver cirrhosis caused by specific etiologies for 204 countries and territories.

Materials and Methods: The data were retrieved from the Global Burden of Disease Study 2019. The age-standardized incidence rate (ASIR), age-standardized prevalence rate (ASPR), age-standardized death rate, and estimated annual percentage changes were used to estimate the trends in incidence, prevalence, and mortality of liver cirrhosis by sex, region, country, and etiology between 2009 and 2019.

Results: From 2009 to 2019, the incident cases of liver cirrhosis increased by 16.7%, from 1.8 million (95% uncertainty interval: 1.5–2.1) to 2.1 million (1.7–2.5), and the prevalent cases increased from 1378.3 million (1275.1–1498.8) to 1691.0 million (1560.9–1845.5). Liver cirrhosis contributed to nearly 1.5 million (1.4–1.6) deaths in 2019, nearly 0.2 million more than in 2009. However, the age-standardized death rate fell from 20.71 (19.79–21.65) per 100,000 population in 2009 to 18.00 (16.80–19.31) per 100,000 population in 2019. In terms of sex, males showed higher ASIR, ASPR, and age-standardized death rate than females. Among the etiologies, the ASIR and ASPR of NAFLD increased markedly, and there was also a modest increase in ASIR and ASPR for HCV and alcohol use. In contrast, the ASIR and ASPR of HBV decreased considerably.

Conclusions: Our finding suggests an increasing burden of liver cirrhosis worldwide but a declining attributed death. A high prevalence and still rising trend of NAFLD and alcohol use-etiology were found in patients with

Yan Lan and Hao Wang contributed equally to this work.

Abbreviations: ASDR, age-standardized death rate; ASIR, age-standardized incidence rate; ASPR, age-standardized prevalence rate; ASR, age-standardized rate; DAA, direct-acting antiviral; EAPC, estimated annual percentage changes; GBD, Global Burden of Disease; SDI, socio-demographic index; UI, uncertainty interval

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cirrhosis globally, although variation was found between regions/countries. These data indicate that efforts to reduce the associated burden need to be improved.

INTRODUCTION

Liver cirrhosis caused more than 1.32 million deaths in 2017, accounting for 2.4% of global deaths.[1] Importantly, in recent studies, liver cirrhosis was revealed to be the 16th leading contributor to global disability-adjusted life-years, and it was the 7th leading cause of disability-adjusted life-years among adults aged 50–74 years, with a considerable impact on human health and quality of life.[2,3]

The etiologies of liver cirrhosis are unevenly distributed among countries. For instance, HBV is the major etiology of liver cirrhosis in China,[4] while Egypt has the highest prevalence of HCV in the world.[5] Meanwhile, alcohol is a significant contributor to the burden of liver cirrhosis in Brazil.[6] Thus, separate global and regional etiology-specific burden analyses of liver cirrhosis are warranted.

Previous studies have analyzed the global burden of liver cirrhosis. For instance, Zhai et al.[7] performed a detailed analysis of the global prevalence of liver cirrhosis and its various etiologies from 1990 to 2017. Moreover, the Global Burden of Disease (GBD) Cirrhosis Collaborators systematically reported liver cirrhosis burden results for 195 countries from 1990 to 2017.[1] Together, these 2 studies show that chronic hepatitis B and C remain a major problem for liver cirrhosis worldwide but that the impact of hepatitis may be mitigated and surpassed by NASH soon. However, neither of the 2 studies reported liver cirrhosis-related incidence. In addition, the latest epidemiological data on liver cirrhosis for the last 2 years is not known. To that end, we conducted a comprehensive and detailed analysis of the incidence, prevalence, and mortality rate of liver cirrhosis and its etiologies for 204 countries from 2009 to 2019 using the latest data from GBD, to provide a reference and theoretical basis for the establishment of public health policies on liver cirrhosis.

MATERIALS AND METHODS

Data source

Annual liver cirrhosis incidence, prevalence, and mortality, as well as corresponding age-standardized rates (ASRs) by sex, region, country, and etiology between 2009 and 2019, were extracted from the Global Health Data Exchange query tool (http://ghdx.healthdata.org/gbd-results-tool). The data were collected from 204 countries and regions and divided into 5 regions (low, low-medium, medium, high-medium, and high) according to the socio-demographic index (SDI). In addition, these countries were geographically divided into 21 regions, including the high-income Asia Pacific and Central Asia (Table 1). The population and disease burden estimation methods for GBD have been described in previous studies.[8] Since the ICD-10 code is not suitable for the etiological estimation of liver cirrhosis, the GBD study used the model to classify the etiology of liver cirrhosis into hepatitis B, hepatitis C, NAFLD, alcohol use, and other causes (autoimmune hepatitis, hemochromatosis, Wilson disease or unknown, etc.).[9]

Statistical analysis

The ASR and estimated annual percent change (EAPC) were used to study incidence, prevalence, and mortality trends in liver cirrhosis to eliminate heterogeneity caused by factors such as sex, age, and population growth. DisMod-MR 2.1, a Bayesian meta-regression tool, was used to pool incidence, prevalence, and mortality data, and generate age-sex-location-year-specific estimates. Liu et al.[10] previously described the calculation of ASR and EAPC. The ASR (per 100,000 population) was calculated directly. The 95% uncertainty interval (UI) represents the 25th and 975th values in all 1000 draws. Analyzing the ASR can provide a better knowledge of the burden of liver cirrhosis as well as additional evaluation of the efficiency of its prevention and therapy. EAPC is an indicator to measure the changing trend of ASR over a period of time, and its value and 95% CI were obtained according to the linear regression model. If the EAPC and upper bound of its 95% CI were both <0, the ASR was considered to be on a downward trend. Conversely, if the EAPC and lower bound of its 95% CI were >0, then the ASR was considered to be on an upward trend. Otherwise, the ASR remained stable over time. In this study, we determined the incidence, prevalence, and mortality rate attributed to liver cirrhosis in different populations in terms of age-standardized incidence rate (ASIR), age-standardized prevalence rate (ASPR), and age-standardized death rate (ASDR), respectively. The SDI is a composite indicator that measures a region's average years of schooling, female total fertility rate under 25 years old, and the lagged distribution of per capita income, and it ranges from 0 (worst) to 1 (best). This study used SDI to assess the relationship between

TABLE 1 ASIR, ASPR, ASDR, and cases of liver cirrhosis by sex, SDI, etiology, and region in 2019

Characteristics	Incident cases, N ×10^3 (95% UI)	ASIR per 100,000, N (95% UI)	Prevalent cases, N ×10^3 (95% UI)	ASPR per 100,000, N (95% UI)	Deaths, N ×10^3 (95% UI)	ASDR per 100,000, N (95% UI)
Overall	2051.6 (1661.4–2478.1)	25.35 (20.78–30.44)	1690958.5 (1560881.6–1845457.6)	20710.05 (19127.33–22589.38)	1472.0 (1374.6–1578.7)	18.00 (16.80–19.31)
Sex						
Male	1206.1 (964.2–1464.6)	29.67 (23.86–35.98)	932427.9 (862829.0–1009411.5)	23139.35 (21465.45–25005.34)	969.1 (899.2–1045.3)	24.81 (23.07–26.75)
Female	845.4 (687.5–1016.9)	20.91 (17.22–25.15)	758530.5 (697316.0–830445.1)	18309.42 (16832.98–20079.08)	502.9 (459.2–550.9)	11.70 (10.68–12.81)
SDI						
Low	233.1 (186.1–284.3)	24.07 (18.49–30.18)	193360.7 (177211.6–209975.8)	22984.36 (21207.12–24934.12)	187.9 (163.8–215.2)	32.78 (28.90–37.11)
Low-middle	439.5 (343–544.1)	25.30 (19.68–31.38)	345616.6 (317472.6–378992.4)	21061.31 (19358.81–23011.88)	376.2 (342.1–416.6)	26.21 (23.86–28.99)
Middle	688.6 (544.1–840.9)	25.76 (20.56–31.34)	622295.4 (575403.3–678195.3)	23751.96 (21962.08–25846.99)	469.6 (427.8–516.8)	19.23 (17.45–21.15)
High-middle	421.1 (340.3–507.3)	24.90 (20.52–29.90)	359707.5 (332262.9–393184.8)	20138.30 (18573.27–21918.63)	251.9 (236.1–269.3)	12.81 (12.00–13.68)
High	268.4 (231.1–305.7)	23.91 (20.82–27.14)	168993.4 (155451.6–184957)	12911.38 (11829.00–14191.67)	185.5 (173.7–196.1)	10.77 (10.23–11.31)
Etiology						
Hepatitis B	405.9 (285.2–536.7)	4.91 (3.46–6.47)	316689.1 (283569.4–350879.8)	3951.47 (3538.09–4384.71)	331.3 (278.5–392.1)	4.03 (3.39–4.76)
Hepatitis C	551.7 (409.3–711.0)	6.67 (4.98–8.56)	112371.5 (91178.7–138096.1)	1414.72 (1146.77–1744.72)	395.0 (335.8–458.6)	4.82 (4.09–5.57)
NAFLD	136.0 (88.6–206.3)	1.63 (1.06–2.45)	1235652.9 (1109502.0–1378481.2)	15022.90 (13493.19–16764.24)	134.2 (96.5–176.9)	1.66 (1.20–2.17)
Alcohol use	436.1 (314.5–579.1)	5.24 (3.78–6.94)	14837.9 (12087.1–18094.3)	176.27 (143.99–214.28)	372.0 (314.7–438.4)	4.48 (3.81–5.28)
Other causes	521.9 (407.2–655.3)	6.90 (5.44–8.55)	11409.8 (9283.1–13880.2)	144.72 (118.45–175.62)	239.5 (188.0–302.9)	3.02 (2.38–3.78)
Region						
High-income Asia Pacific	50.8 (41.6–60.1)	25.15 (21.29–29.18)	28545.7 (26288.0–31008.7)	10779.09 (9892.46–11764.47)	36.9 (32.2–41.1)	8.69 (7.87–9.38)
Central Asia	58.2 (51.5–64.8)	59.06 (52.30–66.01)	20128.7 (18551.7–21815.4)	22013.89 (20401.71–23823.22)	33.9 (30.5–37.7)	42.86 (38.53–47.51)
East Asia	424.4 (321.4–529.8)	22.51 (17.71–27.56)	443382.3 (409948.0–482198.3)	23591.36 (21839.83–25672.38)	164.7 (140.1–191.7)	8.18 (7.01–9.46)
South Asia	414 (299.6–539.3)	22.98 (16.68–29.92)	314219.4 (285628.5–346082.4)	18594.88 (16923.68–20543.18)	348.4 (306.9–404.8)	23.49 (20.74–27.13)
Southeast Asia	181.5 (142.6–219.7)	24.76 (19.5–30.00)	171798.8 (158285.6–187413.6)	24581.50 (22731.41–26747.77)	186.2 (165.4–207.7)	30.21 (26.88–33.49)
Australasia	3.3 (2.8–3.8)	10.26 (8.75–11.72)	4457.6 (4103.1–4822.4)	12249.72 (11234.90–13307.90)	2.5 (2.3–2.7)	5.48 (5.05–5.93)
Caribbean	10.8 (9.2–12.6)	21.85 (18.56–25.08)	9650.8 (8824.5–10515.2)	19180.37 (17538.39–20943.68)	9.5 (7.8–11.4)	18.52 (15.04–22.19)
Central Europe	37.6 (33.2–41.7)	29.11 (25.85–32.45)	21580.5 (19841.6–23490.5)	13958.10 (12779.47–15185.33)	33.6 (29.3–37.9)	17.71 (15.42–20.04)
Eastern Europe	66.9 (47.7–90.0)	31.27 (23.38–41.10)	42176.9 (38868.6–45875.5)	15574.85 (14288.14–17005.89)	72.7 (65.0–81.0)	24.29 (21.67–27.04)
Western Europe	116.2 (102.9–129.2)	24.45 (21.91–26.93)	69332.9 (63545.9–75651.1)	11686.03 (10678.90–12844.73)	77.2 (72.0–82.5)	9.41 (8.93–9.99)
Andean Latin America	20.0 (17.6–22.7)	32.25 (28.40–36.69)	9685.3 (8831.3–10606.3)	15718.95 (14381.11–17138.90)	14.1 (11.2–17.3)	25.08 (20.08–30.92)

TABLE 1. (*continued*)

Characteristics	Incident cases, N $\times 10^3$ (95% UI)	ASIR per 100,000, N (95% UI)	Prevalent cases, N $\times 10^3$ (95% UI)	ASPR per 100,000, N (95% UI)	Deaths, N $\times 10^3$ (95% UI)	ASDR per 100,000, N (95% UI)
Central Latin America	106.2 (85.0–127.9)	40.76 (32.74–48.98)	50155.5 (45767.7–54911.6)	19789.88 (18074.47–21590.20)	68.1 (58.6–78.3)	28.32 (24.45–32.59)
Southern Latin America	22.2 (19.6–24.8)	30.50 (27.07–34.08)	7379.6 (6714.0–8129.8)	9795.27 (8903.97–10797.55)	14.2 (13.2–15.1)	17.34 (16.22–18.49)
Tropical Latin America	50.2 (36.2–65.5)	19.79 (14.41–25.57)	51867.3 (47701.1–56226.6)	20925.42 (19304.50–22674.08)	38.8 (36.5–41.3)	15.72 (14.81–16.75)
North Africa and Middle East	160.1 (133.5–190.7)	28.68 (23.58–34.88)	190404.9 (175183.0–206509.9)	32759.69 (30409.31–35327.86)	109.7 (81.4–135.2)	27.73 (21.06–33.88)
High-income North America	98.6 (81.1–116.8)	25.62 (21.47–30.08)	51570.8 (46810.7–57141.0)	10994.05 (9971.10–12175.12)	72.7 (69.3–75.5)	12.67 (12.16–13.11)
Oceania	1.1 (0.9–1.3)	8.50 (7.05–10.00)	2664.2 (2462.2–2890.7)	24723.95 (22926.71–26739.52)	1.2 (0.9–1.4)	13.19 (10.56–16.35)
Central Sub-Saharan Africa	30.8 (25.7–36.8)	26.97 (21.49–33.11)	24200.2 (22170.7–26374.6)	24977.25 (22992.70–27149.80)	22.8 (17.1–29.1)	36.98 (27.96–47.37)
Eastern Sub-Saharan Africa	86.0 (67.8–105.5)	27.15 (19.80–35.41)	63148.4 (58110.4–68829.1)	21859.79 (20182.87–23683.70)	77.0 (66.3–91.4)	44.15 (38.47–51.91)
Southern Sub-Saharan Africa	12.2 (9.2–15.4)	15.57 (11.70–19.87)	18061.7 (16705.7–19691.8)	24493.23 (22648.59–26517.74)	9.2 (8.2–10.3)	15.43 (13.82–17.16)
Western Sub-Saharan Africa	100.5 (80.8–121.9)	26.22 (19.92–33.23)	96547.1 (89140.2–104636.9)	28242.01 (26254.63–30294.71)	78.7 (61.7–99.8)	37.50 (30.28–46.47)

Abbreviations: ASDR, age-standardized death rate; ASIR, age-standardized incidence rate; ASPR, age-standardized prevalence rate; NAFLD, nonalcoholic fatty liver diseases; SDI, socio-demographic index; UI, uncertainty interval.

regional development level and the incidence, prevalence, and mortality rate of liver cirrhosis. All statistical analyses were performed using R software (Version 4.1.1). This study was approved as exempt by the institutional review board of the First Affiliated Hospital of Zhejiang University.

RESULTS

Global liver cirrhosis burden

Globally, the incident cases of liver cirrhosis reached 2.1 million (95% UI: 1.7–2.5) in 2019, with 1206,100 (964,200–1464,600) cases in males and 845,400 (687,500–1016,900) in females, compared with more than 1.8 million (1.5–2.1) cases for both sexes in 2009 (Table 1, Supplemental Table S1, http://links.lww.com/HC9/A78). The ASIR in 2019 [25.35 (20.78–30.44) per 100,000 population] is similar to that of 2009 [25.17 (21.14–29.52) per 100,000 population]. The ASIR trend between 2009 and 2019 in males and females was similar. The prevalent cases of liver cirrhosis increased from 1378.3 million (1275.1–1498.8) in 2009 to 1691.0 million (1560.9–1845.5) in 2019. Among these, there were 932.4 (862.8–1009.4) million males and 758.5 (697.3–830.4) million females in 2019. The ASPR of liver cirrhosis increased from 20013.38 (18538.93–21734.04) per 100,000 population in 2009 to 20710.05 (19127.33–22589.38) per 100,000 population in 2019. Liver cirrhosis contributed to nearly 1.5 million (1.4–1.6) deaths in 2019, nearly 0.2 million more than in 2009. However, the ASDR fell from 20.71 (19.79–21.65) per 100,000 population in 2009 to 18.00 (16.80–19.31) per 100,000 population in 2019.

Liver cirrhosis burden in different regions

At the regional level, Central Asia had the highest ASIR for liver cirrhosis in 2019 [59.06 (95% UI: 52.30–66.01) per 100,000 population; Table 1], mainly due to alcohol use (35.8% of all liver cirrhosis incidence; Figure 1A). Central Latin America and Andean Latin America had the next highest ASIR, with 40.76 (32.74-48.98) per 100,000 population in Central Latin America and 32.25 (28.40–36.69) per 100,000 population in Andean Latin America. In contrast, Oceania had the lowest ASIR for liver cirrhosis [8.87 (7.46–10.33) per 100,000 population].

In 2019, North Africa and Middle East displayed the highest ASPR of liver cirrhosis, with a rate of 32759.69 (95% UI: 30409.31–35327.86) per 100,000 population, followed by Western Sub-Saharan Africa and Central Sub-Saharan Africa, with NAFLD being the main cause in all 3 regions (84.8%, 43.8%, 46.9% of all liver cirrhosis cases, respectively; Figure 1B). However, the ASPR was lowest in Southern Latin America [9795.27 (8903.97–10797.55) per 100,000 population], high-income Asia Pacific [10779.09 (9892.46–11764.47) per 100,000 population], and high-income North America [10994.05 (9971.1–12175.12) per 100,000 population].

Sub-Saharan Africa had the highest ASDR rates. Eastern, Western, and Central Sub-Saharan Africa had the greatest ASDR of liver cirrhosis in 2019 (from first to third) [with rates of 44.15 (95% UI: 38.47–51.91) per 100,000 population, 37.5 (30.28–46.47) per 100,000 population and 36.98 (27.96–47.37) per 100,000 population, respectively]. In Eastern Sub-Saharan Africa and Central Sub-Saharan Africa, deaths were mainly attributed to hepatitis C (34.6% and 31.5%, respectively), whereas in Western Sub-Saharan Africa, deaths were mainly caused by hepatitis B (43.3%; Figure 1C). In contrast, Australasia had the lowest liver cirrhosis burden with an ASDR of 5.48 (5.05–5.93) per 100,000 population. East Asia had the second-lowest ASDR [8.18 (7.01–9.46) per 100,000 population], followed by the high-income Asia Pacific [8.69 (7.87–9.38) per 100,000 population].

Liver cirrhosis burden in different countries and territories

Among all the countries and territories, The Republic of Moldova had the highest ASIR of liver cirrhosis both in 2009 and 2019, despite displaying a decreasing trend with an EAPC of −2.55 (95% CI: −2.98 to −2.12) (Figure 2A, D). In 2019, 45.9% of the incidence of liver cirrhosis in The Republic of Moldova was caused by alcohol use (Supplemental Table S2, http://links.lww.com/HC9/A78). Mongolia, Egypt, Uzbekistan, and Kazakhstan had high ASIR, with over 60 per 100,000 population. The ASIR was lowest in the Cook Islands and Papua New Guinea. In terms of speed of change, Kazakhstan had the fastest increase in ASIR with 38.9% of the liver cirrhosis cases arising due to alcohol use in 2019. In contrast, the fastest decrease in ASIR was observed in Taiwan (Province of China).

As for the prevalence of liver cirrhosis, Egypt ranked first in ASPR both in 2009 and 2019, the high ASPR was primarily attributed to NAFLD (Figure 2B, Supplemental Table S2, http://links.lww.com/HC9/A78). India, Morocco, China, and the US also had high ASPR. In comparison, Finland had the lowest ASPR of 9005.15 (95% UI: 8205.15-10049.15) per 100,000 population in 2019, followed by Greenland, Argentina, Germany, and Canada. The fastest increase in ASPR was observed in Nepal [EAPC = 0.99 (95% CI: 0.85–1.13)], and the primary cause was NAFLD (Figure 2E). Saint Vincent and the Grenadines had the next fastest increase in ASPR. In comparison, the Republic of Korea had the fastest decrease in ASPR [EAPC = −1.34 (95% CI: −1.88 to −0.80)].

In 2019, the liver cirrhosis burden was highest in Mongolia, with an ASDR of 72.85 (95% UI: 56.88–91.27) per 100,000 population, and the largest

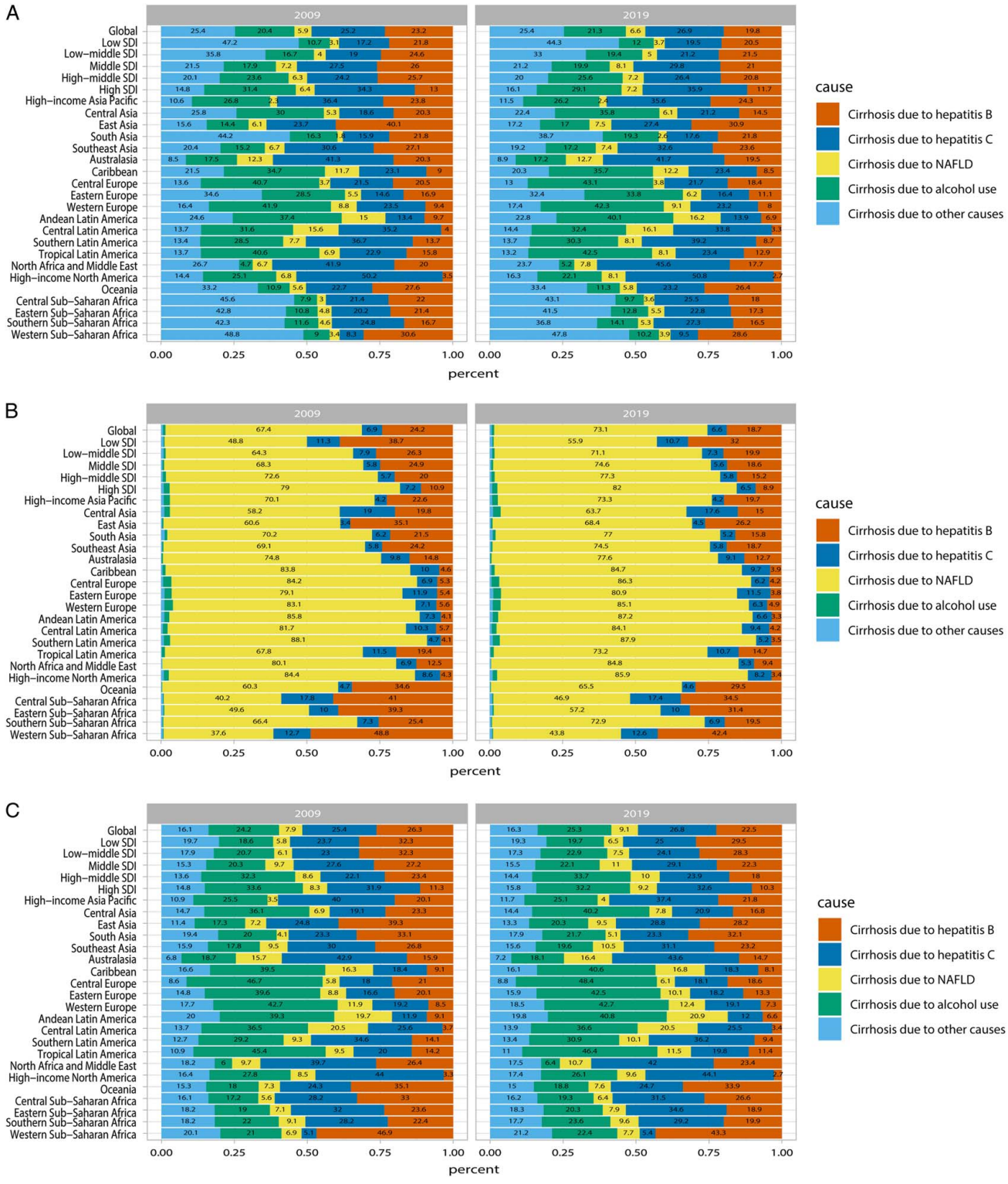

FIGURE 1 Composition ratio of each etiology of liver cirrhosis incident cases, prevalent cases, and deaths in 2009 and 2019. A, Incident cases. B, Prevalent cases. C, Deaths. Abbreviation: SDI, socio-demographic index.

proportion of deaths were attributed to alcohol use (Figure 2C, Supplemental Table S2, http://links.lww.com/HC9/A78). Cambodia and Zambia had the next highest ASDR. Conversely, Malta had the lowest ASDR, followed by Montenegro and the Netherlands. Most countries showed a downward trend in the ASDR of liver cirrhosis. The fastest decrease in ASDR was found in Belarus [EAPC = −5.22 (95% CI: −6.34 to −4.08)], followed by Hungary and China (Figure 2F). However, the Dominican Republic had the fastest

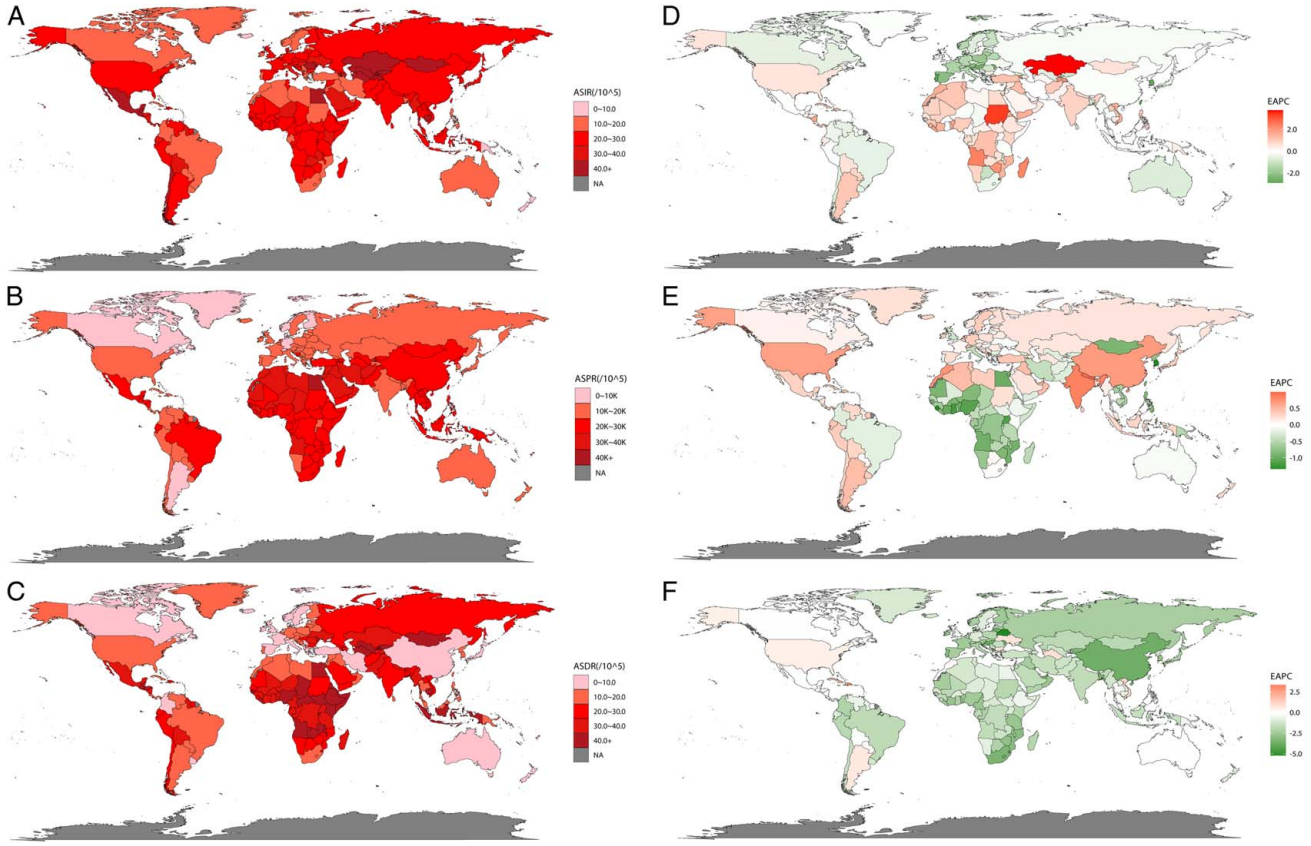

FIGURE 2 The age-standardized rates and EAPC for liver cirrhosis in 204 countries and territories in 2019. A, ASIR. B, ASPR. C, ASDR. D, EAPC of ASIR. E, EAPC of ASPR. F, EAPC of ASDR. Abbreviations: ASDR, age-standardized death rate; ASIR, age-standardized incidence rate; ASPR, Age-standardized prevalence rate; EAPC, estimated annual percentage changes; NA, not applicable.

increase in ASDR, with 39.1% of liver cirrhosis-related deaths caused by alcohol use.

Sex-related differences in liver cirrhosis burden

The ASIR and ASPR of liver cirrhosis in males were nearly 1.5 times higher than in females (Figure 3A, B; Table 1). However, the ASDR of liver cirrhosis in males was over 2 times higher than in females. The total number of liver cirrhosis-related deaths in 2019 was 969100 (95% UI: 899,200–1045,300) for males and 502900 (459,200–550,900) for females. The ASIR, ASPR, and ASDR of liver cirrhosis in all regions in males were significantly higher than in females, except for ASIR in North Africa and Middle East and ASPR in the Caribbean, Central Latin America, and Tropical Latin America, which showed comparable figures between males and females.

The causes of liver cirrhosis differed between males and females. The global ASIR, ASPR, and ASDR in males were significantly higher compared with females in liver cirrhosis caused by HBV, HCV, and alcohol use (Supplemental Figure S1, http://links.lww.com/HC9/A77). However, the ASIR of liver cirrhosis due to NAFLD in females was higher than in males. For instance, the ASIR was 1.82 (95% UI: 1.17–2.71) per 100,000 population in females and 1.43 (0.90–2.23) per 100,000 population in males in 2019. Likewise, the global ASIR and ASPR of liver cirrhosis caused by other causes were lower in males with the rates of 6.69 (5.18–8.49) per 100,000 population and 128.13 (104.37–156.18) per 100,000 population, respectively, compared with 7.10 (5.64–8.74) per 100,000 population and 160.20 (130.80–195.89) per 100,000 population in females in 2019.

SDI-related differences in liver cirrhosis burden

Overall, the ASIR of liver cirrhosis in the low SDI regions showed a slight increase, while the middle SDI regions remained stable, and the high SDI regions showed a downward trend between 2009 and 2019 (Figure 4A). However, Central Asia was an exception, with much higher than expected levels, and showing a significant increase. In comparison, ASPR remained steady in most regions throughout the study period (Figure 4B). In addition, high SDI regions, such as Southern Latin America, Australasia, high-income North America, high-income Asia Pacific, Eastern, Central, and Western

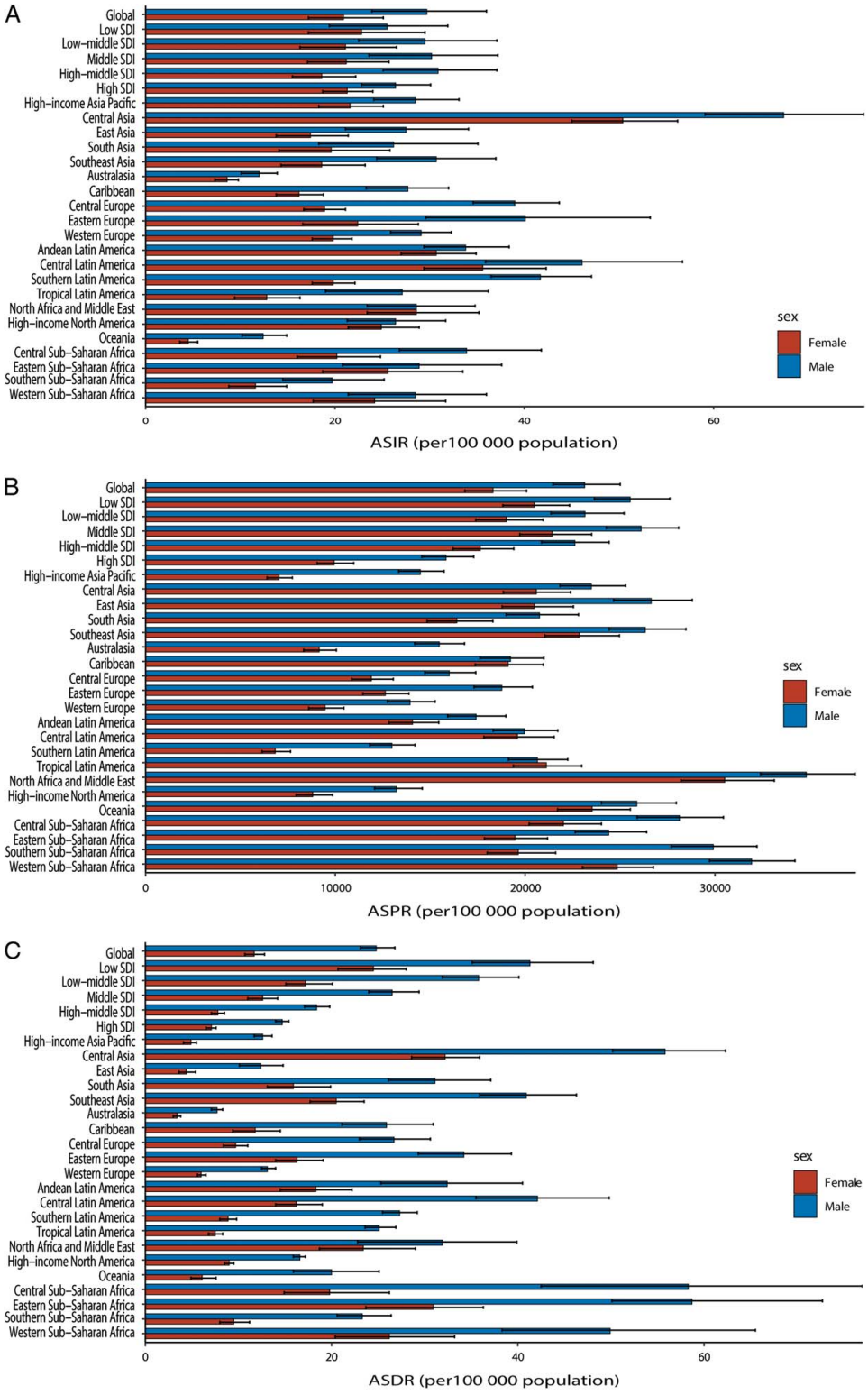

FIGURE 3 The age-standardized rates for liver cirrhosis by region and sex, 2019. A, ASIR. B, ASPR. C, ASDR. Error bars indicate 95% uncertainty intervals for age-standardized rates. Abbreviations: ASDR, age-standardized death rate; ASIR, age-standardized incidence rate; ASPR, age-standardized prevalence rate; SDI, socio-demographic index.

Europe, had lower ASPRs. As for ASDR of liver cirrhosis, most regions had a reduction or remained stable except for Central Asia and the Caribbean (Figure 4C). In general, the ASDR of liver cirrhosis and SDI levels are negatively correlated, as regions with higher SDI levels normally have lower ASDRs. Moreover, different patterns are observed in many medium SDI regions, with some regions remaining

well below-expected levels from 2009 to 2019, while some regions are well above expected levels.

Analysis of liver cirrhosis and its etiologies

Globally, the incident cases of hepatitis B decreased from 415,400 (95% UI: 310,000–529,500) in 2009 to 405,900 (285,200–536,700) in 2019. Correspondingly, the ASIR decreased from 5.81 (4.36–7.41) per 100,000 population in 2009 to 4.91 (3.46–6.47) per 100,000 population in 2019 (Table 1; Supplemental Table S1, http://links.lww.com/HC9/A78). The incident cases of hepatitis B accounted for 19.8% of all cases of liver cirrhosis in 2019 (Figure 1A). The ASIR attributed to hepatitis B ranged from 0.47 (0.3–0.72) per 100,000 population in Jamaica to 9.95 (6.89–13.34) per 100,000 population in Togo (Supplemental Figure S2A, http://links.lww.com/HC9/A77). The highest ASPR was found in Burkina Faso, and the lowest was found in Uruguay. Among countries, the ASDR of liver cirrhosis caused by hepatitis B was highest in Kenya [9.5 (6.5–14) per 100,000 population] and lowest in Colombia [0.22 (0.14–0.34) per 100,000 population]. The ASIR, ASPR, and ASDR for liver cirrhosis due to hepatitis B declined in most countries (Supplemental Figure S3A, http://links.lww.com/HC9/A77).

Hepatitis C accounted for the largest proportion of incident cases and deaths globally in 2019. From 2009 to 2019, the incident cases of hepatitis C increased by 22.7%, from 449,600 (95% UI: 345,100–565,500) to 551,700 (409,300–711,000) and the ASIR increased from 6.28 (4.85–7.90) per 100,000 population to 6.67 (4.98–8.56) per 100,000 population (Table 1; Supplemental Table S1, http://links.lww.com/HC9/A78). The ASIR and ASDR of hepatitis C were the lowest in Iceland and highest in Egypt (Supplemental Figure S2B, http://links.lww.com/HC9/A77). The highest ASPR was found in Mongolia, and the lowest was found in American Samoa. Changes in ASIR of hepatitis C varied by country from 2009 to 2019, the EAPC due to hepatitis C ranged from −3.46 (95% CI: −3.72 to −3.19) in Taiwan (Province of China) to 5.39 (4.55–6.23) in Sudan (Supplemental Figure S3B, http://links.lww.com/HC9/A77). Similarly, the EAPC of ASPR due to hepatitis C ranged from −8.87 (95% CI: −11.21 to −6.48) in Egypt to 6.47 (4.79–8.18) in Iran (the Islamic Republic of Iran).

NAFLD was the least common cause of liver cirrhosis incidence and mortality globally. However, the prevalent cases of liver cirrhosis attributed to NAFLD was as high as 73.1% in 2019 (Figure 1). The prevalent cases of NAFLD increased from 928.3 million (95% UI: 830.3–1038.1) in 2009 to 1235.7 million (1109.5–1378.5) in 2019 (Table 1; Supplemental Table S1, http://links.lww.com/HC9/A78). The highest ASIR of liver cirrhosis due to NAFLD was found in Mexico, but the highest ASPR and ASDR were both found in Egypt (Supplemental Figure S2C, http://links.lww.com/HC9/A77). In terms of ASIR and ASPR of liver cirrhosis due to NAFLD, most countries were on the rise; the fastest increase of ASIR was observed in Sudan [EAPC = 5.45 (95% CI: 4.60–6.30)], and the fastest increase of ASPR was found in China [EAPC = 2.05 (95% CI: 1.64–2.46)]. Comparatively, the Republic of Korea had the fastest decrease in ASIR and ASPR (Supplemental Figure S3C, http://links.lww.com/HC9/A77).

The incident cases of liver cirrhosis due to alcohol consumption increased from 364100 (95% UI: 275,500–462,900) in 2009 to 436,100 (314,500–579,100) in 2019 globally, and the ASIR increased from 5.08 (3.86–6.47) per 100 000 population to 5.24 (3.78–6.94) per 100,000 population (Table 1; Supplemental Table S1, http://links.lww.com/HC9/A78). The Republic of Moldova had the highest ASIR and ASPR of liver cirrhosis due to alcohol use in 2019 (Supplemental Figure S2D, http://links.lww.com/HC9/A77). On the contrary, the lowest ASIR was observed in Papua New Guinea, and the lowest ASPR was found in Sudan. As for ASDR of liver cirrhosis due to alcohol use, it ranged from 0.52 (0.36–0.73) per 100,000 population in Singapore to 29.25 (21.58–38.89) per 100,000 population in Mongolia. The fastest increase in the ASIR and ASPR of liver cirrhosis due to alcohol use was found in Sudan. However, the fastest decrease in ASIR and ASPR was observed in Taiwan (Province of China). Importantly, ASDR of liver cirrhosis caused by alcohol use declined in most countries, with EAPC ranging from −5.12 (95% CI: −6.25 to −3.97) in Belarus to 3.59 (2.98–4.2) in the Dominican Republic (Supplemental Figure S3D, http://links.lww.com/HC9/A77).

The proportion of other causes in the global incident cases of liver cirrhosis remained stable from 2009 to 2019, and the incident cases increased from 453,200 (95% UI: 361,900–556,100)) in 2009 to 521,900 (407,200–655,300) in 2019 (Table 1; Supplemental Table S1, http://links.lww.com/HC9/A78). The lowest ASIR, ASPR, and ASDR of liver cirrhosis due to other causes were both observed in New Zealand. Conversely, Turkmenistan had the highest ASIR and ASPR of liver cirrhosis due to other causes, and Egypt had the highest ASDR (Supplemental Figure S2E, http://links.lww.com/HC9/A77). As for the ASR of liver cirrhosis due to other causes, the fastest increase in ASIR and ASPR was observed in Sudan, and the fastest increase in ASDR was detected in the Dominican Republic. In comparison, Taiwan (Province of China) had the fastest decrease in ASIR and ASPR, while the United Arab Emirates had the fastest decrease in ASDR (Supplemental Figure S3E, http://links.lww.com/HC9/A77).

DISCUSSION

Liver cirrhosis is a major health concern globally. This study reports the incidence, prevalence, and mortality trends of liver cirrhosis and its etiologies in terms of

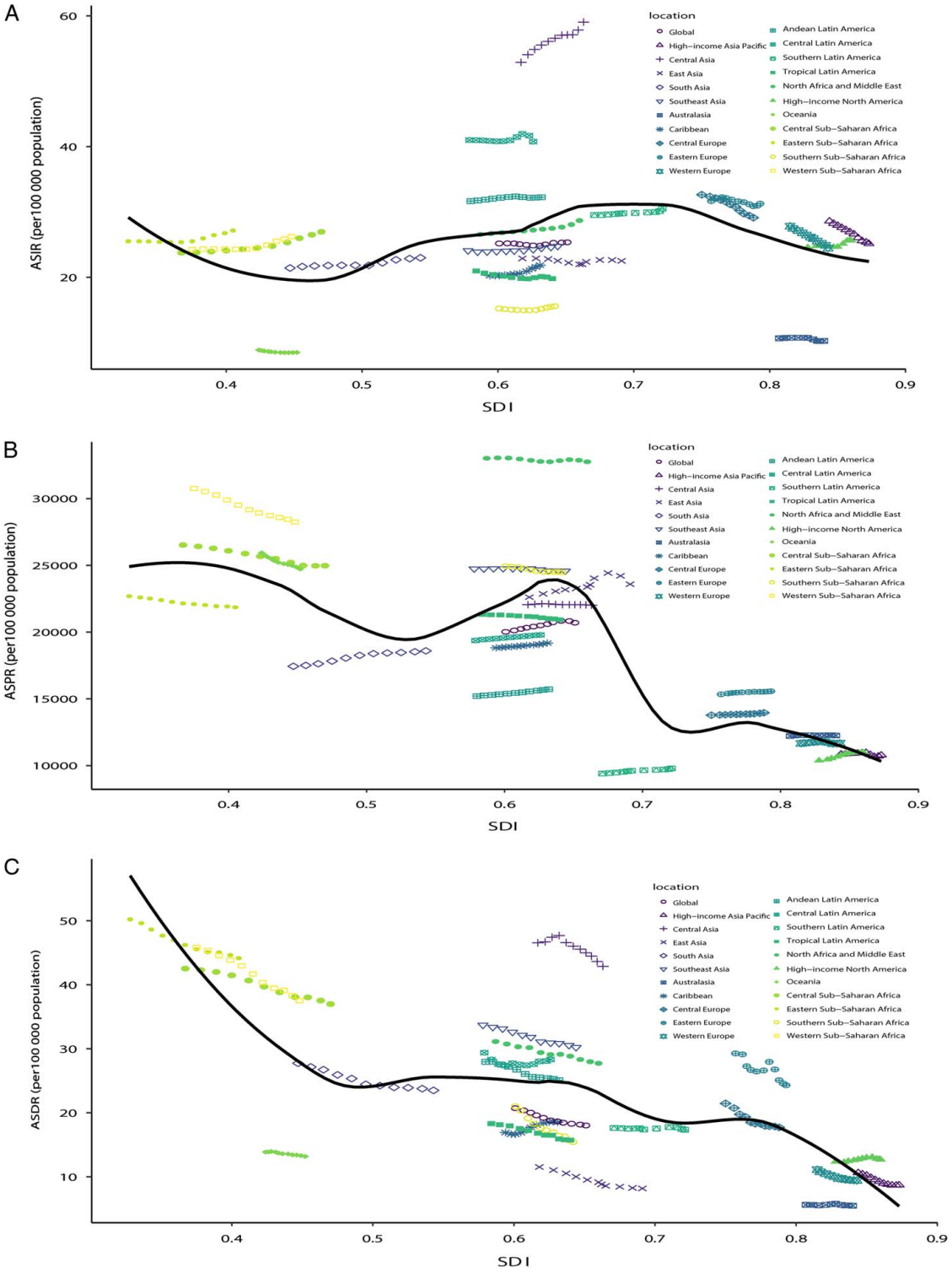

FIGURE 4 The age-standardized rates of liver cirrhosis globally and for 21 regions by SDI, 2009–2019. A, ASIR per 100,000 population. B, ASPR per 100,0000 population. C, ASDR per 100,000 population. For each region, the dots from left to right depict the estimated values for each year from 2009 to 2019. The black line shows the expected incidence, prevalence, or mortality rate based on SDI alone. Abbreviations: ASDR, age-standardized death rate; ASIR, age-standardized incidence rate; ASPR, age-standardized prevalence rate; SDI, socio-demographic index.

country, region, sex, and SDI levels from 2009 to 2019. From the changes in the incidence and number of liver cirrhosis-associated deaths, which can help us understand the effects of current prevention and treatment as well as provide the theoretical basis for formulating public policies. Our study uncovered an increase in the incidence, prevalence, and deaths of liver cirrhosis globally from 2009 to 2019, mainly due to an increasing

and aging global population.[11] The global burden of liver cirrhosis in males is much greater than in females, mainly due to higher HBV, HCV, and alcohol use. In NAFLD, females have higher ASIR but lower ASPR and ASDR than males, which is mainly related to higher rates of obesity and the protective effects of estrogen in females.[12] In addition, gender differences in liver cirrhosis are also associated with higher risk factor behaviors such as drug injection and higher alcohol consumption in males.[13]

Our study showed that ASIR in liver cirrhosis remained stable from 2009 to 2019 and was not significantly associated with SDI levels. However, Central Asia is an exception, with the highest ASIR as a result of their higher alcohol use.[14] Due to socio-economic and medical advancements, the ASDR is decreasing in most regions. In addition, high-income countries such as the high-income Asia Pacific and western Europe have lower ASPRs and ASDRs, since they benefit from better medical equipment and effective measures, which is broadly in accordance with results of GBD 2017.[1,15]

Our study found that HBV is the main etiology for liver cirrhosis in East Asia. This is mainly due to the large HBV population in China. In China, the number of people with liver cirrhosis caused by HBV accounted for more than 40% of all people with liver cirrhosis in 2009. However, with hepatitis B vaccination, the incidence of HBV has gradually decreased. In 2019, HBV accounted for about 30% of liver cirrhosis incident cases, with HBV remaining a significant burden in China, and immunization coverage still needs to be enforced.[16] Since the lack of finance, medical resources, and lack of awareness of the disease, HBV is most prevalent in low SDI regions, which is a major challenge in Southeast Asia.[17] Fortunately, the ASIR, ASPR, and ASDR of HBV in most countries globally have achieved a general decline, by the increasing availability of antiviral drugs, implementation of public policies with the goal of eliminating viral hepatitis by 2030 and the strong measures taken by several countries.[18] However, a recent epidemiology study indicated that up to 2019, only 68 countries had achieved the goal of reducing HBV-related disease mortality to $\leq$4 deaths per 100,000 people per year, thereby, HBV-related cirrhosis is still a significant burden in the ongoing future.[19]

HCV is another major etiology of liver cirrhosis. Our study showed that Egypt had the highest ASIR and ASDR for HCV liver cirrhosis in 2019, mainly due to inadequate infection control and iatrogenic exposure.[20] Interestingly, the fastest decline in ASPR in liver cirrhosis due to HCV from 2009 to 2019 was also detected in Egypt. It was believed that the implementation of the early screening program and the wide availability of HCV eradication therapy, significantly reduced the prevalence of the HCV-positive population.[21,22] Since Taiwan (Province of China) implemented the viral hepatitis program in 2003, almost all patients with viral hepatitis can be reimbursed for antiviral treatment, so Taiwan's ASIR declined the fastest from 2009 to 2019.[23] However, our study found that ASIR and ASPR for liver cirrhosis due to HCV in China Mainland showed an increasing trend, which is consistent with previous studies, and may be due to the relatively delayed initiation of the HCV screening program and the variety of HCV infection routes in these years.[24,25] It can be expected that the incidence and prevalence of HCV-related cirrhosis in China Mainland would decline in the next 5 years, as estimated by the trajectory of HCV epidemiology in Egypt.

With the global increase in the prevalence of obesity and diabetes, NAFLD is the leading cause of liver disease globally.[26] Our study found that the ASIR of liver cirrhosis due to HBV decreased while the ASIR of NAFLD increased, and hepatitis caused the highest proportion of liver cirrhosis deaths, while NAFLD caused the lowest proportion, so more and more NAFLD patients progress to liver cirrhosis over time, making NAFLD the predominant cause of the liver cirrhosis prevalence. This is consistent with previous studies.[7] Among the 21 regions, North Africa and the Middle East had the highest ASPR, as confirmed by Younossi et al.[27] Among the countries, the highest ASPR and ASDR were observed in Egypt, which is in line with the recent study.[28] What's more, China is the one with the fastest increase in the ASPR of NAFLD, which is mainly related to the increasing prevalence of obesity. According to relevant study reports, the prevalence of NAFLD in China will increase by about 30% by 2030.[29] Given this problem, efficiently oriented intervention and prevention strategies are essential for Egypt and China. It is noteworthy that ASDR for liver cirrhosis is declining in most countries, but rising in the US, as reported in the previous studies.[28,30] Further, our study found that among the etiologies, patients with NAFLD-related liver cirrhosis represented the most increase in ASDR, which may be related to genetics, the environment, unhealthy lifestyle, high prevalence of obesity and diabetes, and also partially due to lack of specific treatment and intervention measures.[31] Also, increased awareness and advanced diagnostic approach for death caused by NAFLD-related liver cirrhosis in the US may be an alternative explanation.[32]

Our findings showed that alcohol is the leading etiology for the high incidence and mortality in most European and Latin American regions, correlating with their high alcohol intake, with the global distribution of liver cirrhosis due to alcohol use being consistent with the distribution of alcohol consumption.[33] For instance, alcohol is the largest contributor to incidence and deaths from liver cirrhosis in Brazil, in line with previous studies.[6] Our study also found an upward trend in ASIR and ASPR for liver cirrhosis caused by alcohol use in Asia from 2009 to 2019, which is consistent with the

study by Suthat et al.[14] Conversely, North Africa and the Middle East had the lowest ASIR, ASPR, and ASDR among the 21 regions, largely due to religious and cultural beliefs prohibiting alcohol consumption in some of these regions.[34] A previous study has found that the harm caused by alcohol can be reduced through taxes and regulations.[35] Therefore, some middle-high and high-SDI regions should actively take measures to reduce alcohol intake by increasing alcohol consumption tax, controlling alcohol supply, etc.

Other causes are the main etiology for the incidence of liver cirrhosis in low SDI regions such as Sub-Saharan Africa, which is mainly attributed to Sub-Saharan Africa's poor economic development, poor sanitation, and lack of medical resources, leading to hepatitis E and schistosomiasis and other diseases.[34] In addition, patients in Sub-Saharan Africa do not seek medical attention until the advanced stages of liver cirrhosis, and the mortality rate is high, which requires the attention of the local government to implement appropriate countermeasures.[36]

Limitations

Similar to other GBD studies, the main limitation of this study lies in the accuracy of the original data. The data of some economically underdeveloped areas are not fully reported, underestimating the true burden of liver cirrhosis. Second, the liver cirrhosis in the GBD data does not distinguish between compensated and decompensated stages, and the difference between the 2 cannot be further analyzed and compared. In addition, we can only evaluate each etiology of liver cirrhosis independently and cannot investigate interactions between etiologies, such as liver cirrhosis caused by concurrent HBV and HCV infections.

Future directions

From the results presented herein, first, the impact of the etiology-specific intervention on the changing epidemiology of liver cirrhosis needs to be further investigated. For example, it has been reported a steep decline in the HCV-related mortality rate in Egypt during the direct-acting antiviral (DAA) era. The China Mainland, where the wide-use of DAA was later than in Egypt, represents a good field to confirm the sustained effect of DAA on the epidemiology of HCV-related liver cirrhosis. Second, the etiology and ethnicity-specific epidemiology of liver cirrhosis needs to be further investigated. A rising trend in the incidence of NAFLD-related cirrhosis is present in most countries and increasing mortality in some countries. The identification of driving factors of increasing ASDR of NAFLD-related cirrhosis would help design specific intervention strategies to reduce mortality. And it has been reported that the burden of end-stage liver diseases was distinct among different ethnicities. In addition, disparities in care and access to new treatments should be studied further.

CONCLUSIONS

The ASDR of liver cirrhosis has decreased globally from 2009 to 2019. The prevalence of HBV has declined substantially, but HCV remains a major challenge in some regions. Furthermore, ASIR and ASPR for NAFLD, alcohol consumption and other causes of liver cirrhosis are increasing, with the most substantial increase in NAFLD. As a result, liver cirrhosis remains a major global burden and countries are thus encouraged to take prompt action to implement targeted measures, depending on their most common etiology of liver cirrhosis.

AUTHOR CONTRIBUTIONS

Yan Lan and Haoda Weng: collected the data and performed the statistical analysis. Yan Lan and Hao Wang, Xianbin Xu, Xia Yu, Huilan Tu, Kai Gong, Junjie Yao, and Shaoheng Ye: analyzed results. Yan Lan: drafted the manuscript. Jifang Sheng and Yu Shi: revised the draft. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declared that there was no potential conflict of interest.

AVAILABILITY OF DATA AND MATERIALS

The data sets generated and/or analyzed during the current study are available in the GBD repository (http://ghdx.healthdata.org/gbd-results-tool).

CONSENT FOR PUBLICATION

Not applicable.

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