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The Global Burden of Cirrhosis and Other Chronic Liver Diseases in 2021

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ABSTRACT

Background and Aim: The burden of cirrhosis and other chronic liver diseases has changed in recent years due to shifts in the contributing aetiologies. We estimated the burden of cirrhosis and other chronic liver diseases, including etiological and regional differences, across 204 countries and territories from 2010 to 2021.

Approach and Results: We analysed temporal trends in the burden of cirrhosis and other chronic liver diseases utilising data from the Global Burden of Disease Study 2021. We estimated annual frequencies and age-standardised rates (ASRs) of incident cases, deaths and disability-adjusted life-years (DALYs) by sex, country, World Health Organisation region and its contributing aetiologies. In 2021, there were an estimated 58 417 006 incident cases, 1 425 142 deaths and 46 417 777 DALYs related to cirrhosis and other chronic liver diseases. From 2010 to 2021, there was a rise in age-standardised incidence rates (ASIRs) (APC: +0.35%) but age-standardised death rates (ASDRs) (APC: −1.74%) and age-standardised disability-adjusted life-years (ASDALYs) (APC: −1.85%) declined. Cirrhosis related to metabolic dysfunction-associated steatohepatitis (MASH) contributed to 48 310 981 incident cases in 2021 and was largely responsible for the overall increase in ASIRs from 2010 to 2021. Cirrhosis and other chronic liver diseases related to MASH were the only aetiology with a rise in ASIR (APC: +0.86%). Age-standardised deaths related to

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all aetiologies of cirrhosis and other chronic liver diseases declined during the study period. Age-standardised deaths and DALYs related to MASH increased in the Americas, unlike all other world regions where they declined or remained stable.
Conclusions: Age-adjusted deaths related to cirrhosis and other chronic liver diseases are declining. However, the age-adjusted incidence of cirrhosis and other chronic liver diseases is increasing, driven by increases in the incidence of MASH.

1 | Introduction

Cirrhosis and chronic liver disease are major global health concerns, ranking among the top 10 leading causes of death in Africa, Southeast Asia, Europe and the eastern Mediterranean in 2023 [1]. The primary causes of cirrhosis and other chronic liver diseases include hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol-related liver disease (ALD) and metabolic dysfunction-associated steatohepatitis (MASH) [2]. However, the epidemiology of the causes of liver diseases has changed dramatically in the recent decade [3].

The burden of HBV is declining largely due to successful vaccination programs and the increasing availability of effective antiviral therapy [4]. However, antiviral coverage remains poor in many regions, with the World Health Organisation (WHO) estimating that only 2.6% of all people with HBV receive antiviral therapy [5]. For HCV, direct-acting antivirals (DAAs), which were introduced in the past decade, have made HCV cure possible for the vast majority of patients [6–8]. However, the effectiveness of DAAs has been hampered by limited accessibility, with only 20% of infected patients receiving therapy [5]. In contrast, ALD has seen a significant rise in mortality [9] and remains the leading cause of alcohol-related deaths worldwide [10, 11]. The COVID-19 pandemic has exacerbated this issue, with studies reporting a 24% increase in alcohol consumption among patients with alcohol use disorder (AUD). MASH, previously known as non-alcoholic steatohepatitis (NASH) [12], is the inflammatory form of metabolic-dysfunction-associated steatotic liver disease (MASLD) that can progress to cirrhosis and liver cancer [13]. The prevalence of MASLD has grown rapidly, increasing from 17.6% in 1990 to 23.4% in 2019, making it one of the most prominent liver diseases in recent years [14].

These changes in the underlying causes of liver disease have led to a corresponding shift in the landscape of cirrhosis and other chronic liver diseases. There are limited data from a global perspective utilising the Global Burden of Disease Study 2021 (GBD 2021). Therefore, we provide updated estimates on the incidence, deaths and disability-adjusted life years (DALYs) related to cirrhosis and other chronic liver diseases, as well as the contributing liver aetiologies across 204 countries and territories from 2010 to 2021.

2 | Methods

2.1 | Data Source

This study used data from the GBD 2021 [15]. The GBD 2021 study provides estimates for 371 diseases and injuries in 204 countries and territories. Information on incidence, deaths and DALYs, including stratification into SDI and WHO region [15], were obtained using the Global Health Data Exchange (GHDx) query tool (http://ghdx.healthdata.org/gbd-results-tool), which is a data catalogue created and supported by the Institute for Health Metrics and Evaluation (IHME).

2.2 | Estimation Methods

In the GBD study, cirrhosis and other chronic liver diseases were divided into five main aetiologies. This included cirrhosis and other chronic liver diseases due to alcohol use, chronic hepatitis B, chronic hepatitis C, non-alcoholic fatty liver disease and cirrhosis related to other causes [16]. Notable diseases from 'cirrhosis related to other causes' included autoimmune hepatitis, toxic liver disease, other forms of inflammatory liver disease and non-specific chronic hepatitis [16]. Recent studies have demonstrated concordance between NAFLD and MASLD [17] and therefore term 'non-alcoholic fatty liver disease' and data collected in this category were classified and referred to using the new nomenclature of MASLD [18]. General estimation methods for the GBD 2021 have been previously described. Data sources were identified from vital registration, verbal autopsy, registry, survey, police or surveillance data across all countries and territories [15]. For GBD 2021, improvements were made upon previous studies; this included updated Bayesian algorithms to reduce noise and implementation of a non-zero floor to address distorted shapes and trends [19]. In addition, COVID-19 estimates and other pandemic-related mortalities (OPRMs) were included as new additions in GBD 2021 [15].

Incidences were modelled using DisMod-MR 2.1 (Disease Modelling Meta-Regression; version 2.1), which is a Bayesian disease modelling meta-regression tool that generates estimates of values such as incidence, prevalence, remission and others [15]. However, for some causes, spatiotemporal Gaussian process regression (ST-GPR) disease models were used instead of DisMod-MR 2 [15]. For mortality estimates, GBD 2021 uses the ICD, 11th edition, whereby each death is assigned to the underlying cause that initiated events leading to death. Cause-of-death estimates were modelled via the Cause of Death Ensemble model (CODEm), which uses an ensemble of statistical models while also systematically testing combinations of covariates based on their out-of-sample predictive validity [15, 19]. It then combines results to estimate deaths by location, age, sex and year for a given cause. The cause-of-death database could only estimate overall cirrhosis and other chronic liver diseases and not its five causes. Instead, DisMod-MR 2.1 splits the parent cirrhosis and other chronic liver disease mortality estimates and used liver cancer aetiological proportion models as covariates [16]. DALY estimates for GBD 2021 were informed by 100983 data sources (including 19189 sources newly used in 2021) [15]. Years lived with disability (YLDs) and years of life lost (YLLs) were summed to calculate DALYs by location, age, sex, year and cause [15].

Summary

- The global burden of cirrhosis and chronic liver diseases is changing.
- Despite a general decline in age-adjusted deaths, there has been an increase in age-adjusted incidence, which is largely attributed to the increasing incidence of metabolic dysfunction-associated steatohepatitis.

Sociodemographic index (SDI) is a composite indicator representing the geometric mean of three parameters: the lag-distributed income per capita, average years of schooling and the fertility rate in females younger than 25 years for a given location [15]. SDI scores were rescaled from 0 (lowest income and years of schooling, and highest fertility) to 100 (highest income and years of schooling, and lowest fertility) [15].

GBD 2021 metrics were estimated as counts, all-age and age-specific rates per 100 000 population, and age-standardised rates per 100 000 population, calculated using the GBD standard population structure. All calculations were conducted 500 times to generate draw-level estimates [15].

2.3 | Statistical Analysis

Final estimates represent the mean estimate across 500 draws, and 95% uncertainty intervals (UIs) are represented by the 2·fifth and 97·fifth percentile values across the draws [15]. Uncertainty was propagated at each step in the estimation process.

The Joinpoint Regression Programme 5.2.0 was used to obtain annual percent change (APC) and its respective 95% confidence interval. When the annualised rate of change and the lower boundary of its 95% CI were both positive, this was considered

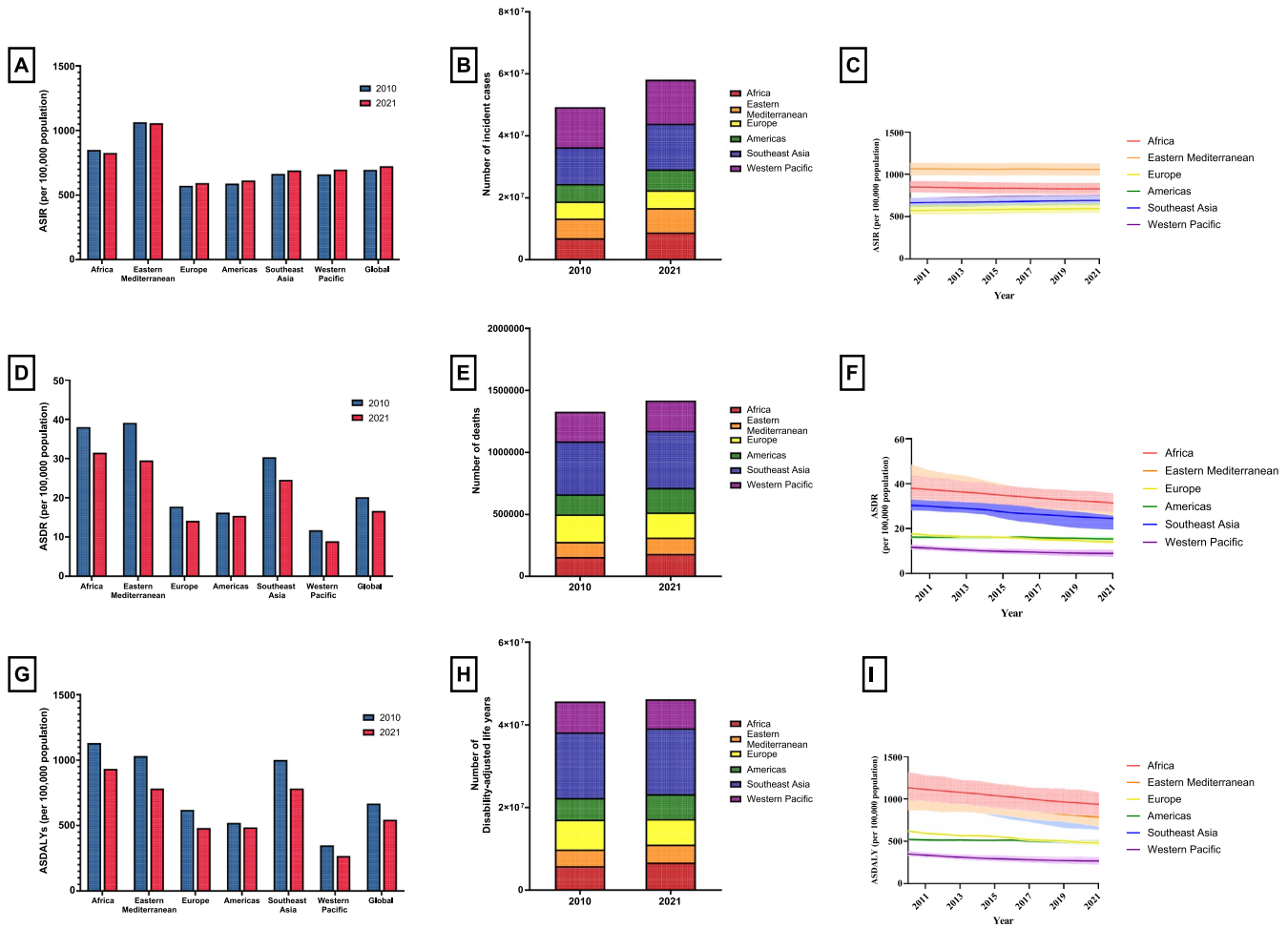

FIGURE 1 | Global incident cases/age-standardised incident rates, deaths/age-standardised death rates and DALYs/age-standardised DALYs rates of cirrhosis and other chronic liver diseases from 2010 to 2021, stratified by WHO region. (A) Age-standardised incident rates due to cirrhosis and other chronic liver diseases in 2010 and 2021, split by the WHO region. (B) Contribution by WHO region of incident cases due to cirrhosis and other chronic liver diseases in 2010 and 2021. (C) Trends in age-standardised incident rates due to cirrhosis and other chronic liver diseases from 2010 to 2021, split by the WHO region. (D) Age-standardised death rates due to cirrhosis and other chronic liver diseases in 2010 and 2021, split by the WHO region. (E) Contribution by the WHO region of deaths due to cirrhosis and other chronic liver diseases in 2010 and 2021. (F) Trends in age-standardised death rates due to cirrhosis and other chronic liver diseases from 2010 to 2021, split by the WHO region. (G) Age-standardised DALYs due to cirrhosis and other chronic liver diseases in 2010 and 2021, split by the WHO region. (H) Contribution by the WHO region of DALYs due to cirrhosis and other chronic liver diseases in 2010 and 2021. (I) Trends in age-standardised DALYs due to cirrhosis and other chronic liver diseases from 2010 to 2021, split by the WHO region.

an increasing trend. By contrast, when the annualised rate of change and the upper boundary were negative, this was considered as a decreasing trend. Results with a p-value ≤ 0.05 were considered statistically significant. Percentage change between 2010 and 2021 within any group was calculated as (value in 2021—value in 2010)/value in 2010.

3 | Results

3.1 | Global Burden of Cirrhosis and Other Chronic Liver Diseases in 2021

Globally, in 2021, there were an estimated 58 417 006 (95% UI: 54231381–62 796 051) incident cases, 1 425 142 (95% UI: 1308121–1 563 089) deaths and 46 417 777 (95% UI: 43056397–50 687 931) DALYs related to cirrhosis and other chronic liver diseases (Supporting Information S1–S3). In 2021, the age-standardised incident rates (ASIRs), age-standardised death rates (ASDRs) and age-standardised disability-adjusted life years (ASDALYs) were 724.31 per 100 000 population (95% UI: 672.98–779.55), 16.64 per 100 000 population (95% UI: 15.28–18.26) and 545.07 per 100 000 population (95% UI: 506.31–594.99), respectively. Between 2010 and 2021, there was a +18% increase in incident cases, a +7% increase in deaths and a +1% increase in DALYs. During the study period, ASIRs increased (APC: +0.35%, 95% CI: 0.30 to 0.40; $p < 0.001$), but the ASDRs (APC: −1.74%, 95% CI: −1.81 to −1.67; $p < 0.001$) and ASDALYs (APC: −1.85%, 95% CI: −1.92 to −1.77; $p < 0.001$) declined. In addition, for all three APC graphs (Supporting Information S4), there was a slight rise in recent years, especially from 2018 to 2021.

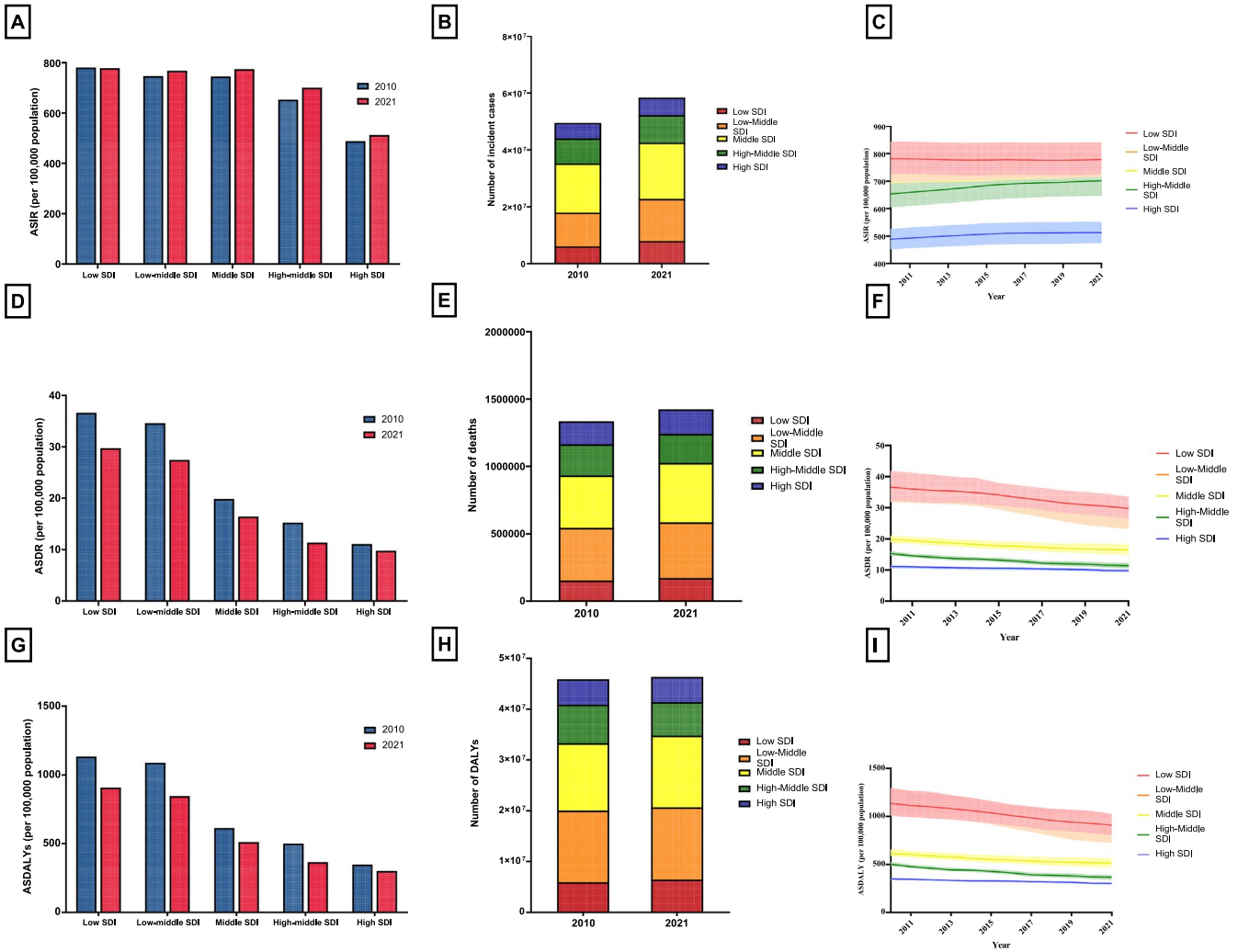

FIGURE 2 | Global/age-standardised incident rates, deaths/age-standardised death rates and DALYs/age-standardised DALYs rates of cirrhosis and other chronic liver diseases from 2010 to 2021, stratified by SDI. (A) Age-standardised incident rates due to cirrhosis and other chronic liver diseases in 2010 and 2021, split by SDI. (B) Contribution by SDI of incident cases due to cirrhosis and other chronic liver diseases in 2010 and 2021. (C) Trends in age-standardised incident rates due to cirrhosis and other chronic liver diseases from 2010 to 2021, split by SDI. (D) Age-standardised death rates due to cirrhosis and other chronic liver diseases in 2010 and 2021, split by SDI. (E) Contribution by SDI of deaths due to cirrhosis and other chronic liver diseases in 2010 and 2021. (F) Trends in age-standardised death rates due to cirrhosis and other chronic liver diseases from 2010 to 2021, split by SDI. (G) Age-standardised DALYs due to cirrhosis and other chronic liver diseases in 2010 and 2021, split by SDI. (H) Contribution by SDI of DALYs due to cirrhosis and other chronic liver diseases in 2010 and 2021. (I) Trends in age-standardised DALYs due to cirrhosis and other chronic liver diseases from 2010 to 2021, split by SDI.

3.2 | Burden of Cirrhosis and Other Chronic Liver Diseases by WHO Region

The incident cases, deaths and DALYs of cirrhosis and other chronic liver diseases by WHO regions are summarised in Supporting Information S1–S3 and Figure 1. Southeast Asia had the highest number of incident cases (14 809 109; 95% UI: 13658110–16 064 676), deaths (460 403; 95% UI: 370585–562 696) and DALYs (15 924 598; 95% UI: 12975188—19 492 194) related to cirrhosis and other chronic liver diseases. However, for age-standardised rates, eastern Mediterranean had the highest ASIR of 1057.21 (95% UI: 986.21–1125.43) per 100 000, while Africa had the highest ASDRs (31.44 per 100 000 population, 95% UI: 27.61–35.62) and the highest ASDALYs (933.8 per 100 000 population, 95% UI: 796.55–1074.47). From 2010 to 2021, the Americas had the greatest increase in the number of deaths (+22%) and DALYs (+16%), whereas Africa had the highest increase in incident cases (+27%).

From 2010 to 2021, there was an increase in ASIRs in Europe, the Americas, Southeast Asia and the western Pacific, with the greatest increase in the western Pacific of APC: +0.49%, 95% CI: 0.44 to 0.55; $p < 0.001$. ASIRs declined in Africa (APC: −0.26%, 95% CI: −0.34 to −0.17; $p < 0.001$) and the eastern Mediterranean region (APC: −0.05%, 95% CI: −0.07 to −0.02; $p = 0.002$). During the study period, ASDRs and ASDALYs declined in all world regions. The greatest decline in ASDR (APC: −2.5%, 95% CI: −2.72 to −2.27; $p < 0.001$) and ASDALYs (APC: −2.46%, 95% CI: −2.65 to −2.27; $p < 0.001$) occurred in the eastern Mediterranean region (Figure 1F,I).

3.3 | Burden of Cirrhosis and Other Chronic Liver Diseases by SDI

Middle SDI countries had the highest incident cases (19 806 401; 95% UI: 18363991–21 307 955) and deaths (441 526; 95% UI: 403365–485 997) related to cirrhosis and other chronic liver diseases, but low SDI countries had the highest ASIRs (778.48 per 100 000 population, 95% UI: 725.4–841.1) and ASDRs (29.74, 95% UI: 26.54–33.48) per 100 000 and ASDALYs of 907.41 (95% UI: 807.08–1024) per 100 000 (Supporting Information S1–S3). The low DI countries had the greatest percentage increase in incident cases (+30%) and DALYs (+9%) (Figure 2B,H), whereas the middle SDI countries had the largest percentage increase in the number of deaths (+14%) (Figure 2E). For the rate of both deaths and DALYs, all SDI groups showed a declining trend with negative APC values. The greatest decline in ASDRs (APC: −2.70%, 95% CI: −3.17 to −2.23; $p < 0.001$) and ASDALYs (APC: −2.94%, 95% CI: −3.47 to −2.4; $p < 0.001$) occurred in high–middle SDI countries.

3.4 | Burden of Cirrhosis and Other Chronic Liver Diseases by Gender

Males experienced higher ASIR (767.36; 95% UI: 714.63–823.52), ASDR (23.13; 95% UI: 21.12–25.52) and ASDALY (762.35; 95% UI: 702.4–846.3) compared to females (Supporting Information S1–S3). When broken down to specific aetiologies, ASIR, ASDR and ASDALY cirrhosis and other chronic liver diseases due to alcoholic, HBV and HCV were much higher in males (Figure 3, Supporting Information S5–S7).

3.5 | Burden of Cirrhosis and Other Chronic Liver Diseases by Country/Territory

The ASDRs related to cirrhosis and other chronic liver diseases in each country/territory in 2021 are summarised in Figure 4. Moldova (ASDR: 75.4, 95% UI: 67.89–83.64), Romania (ASDR: 55.61, 95% UI: 48.96–61.65) and Turkmenistan (51.55, 95% UI: 40.78–64.51) were the countries with the highest ASDR values (Supporting Information S8). ASIRs and ASDALYs in each country/territory in 2021 are also summarised in Figure 4.

3.6 | Trends in the Aetiologies of Cirrhosis and Other Chronic Liver Diseases

MASH had the greatest number of incident cases (48 310 981; 95% UI: 4419137–52 313 165) and ASIRs (592.78, 95% UI: 542.23–643.24) per 100 000. For deaths and DALYs, the most significant

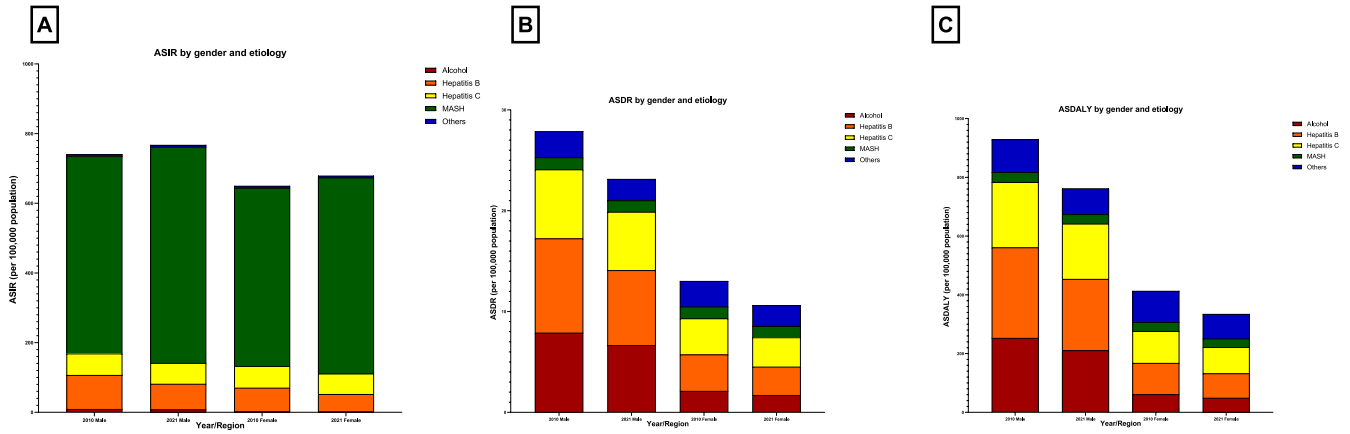

FIGURE 3 | Global age-standardised incident rates, age-standardised death rates and age-standardised DALYs rates of cirrhosis and other chronic liver diseases from 2010 to 2021, stratified by gender. (A) Age-standardised incident rates due to cirrhosis and other chronic liver diseases in 2010 and 2021, split by SDI. (B) Age-standardised death rates due to cirrhosis and other chronic liver diseases in 2010 and 2021, split by SDI. (C) Age-standardised DALY due to cirrhosis and other chronic liver diseases in 2010 and 2021, split by SDI.

contributor was cirrhosis due to hepatitis B with 431 964 (95% UI: 365199–502 419) deaths and 13 882 280 (95% UI: 11749493—15 998 380) DALYs (Supporting Information S1–S3, Figure 5). Between 2010 and 2021, cirrhosis due to MASH had the highest percentage increase in incidence (+24%), deaths (+27%) and DALYs (+23%).

ASIR declined in all aetiologies aside from cirrhosis due to MASH (APC: +0.86%, 95% CI: 0.82 to 0.90; $p < 0.001$) (Figure 5C), with cirrhosis due to HBV experiencing the greatest decrease (APC: −2.72%, 95% CI: −3 to −2.44; $p < 0.001$). All aetiologies also experienced a decrease in ASDR and ASDALY (Figure 5F,I). Cirrhosis due to HBV had the largest decrease in ASDRs (APC: −2.14%, 95% CI: −2.23 to −2.04; $p < 0.001$), whereas ASDALYs was most significantly decreased in cirrhosis due to other causes (APC: −2.19%, 95% CI: −2.36 to −2.01; $p < 0.001$).

When further stratified by WHO regions (Figure 6, Supporting Information S9–S11), Africa had a significantly higher ASIR for cirrhosis related to HBV (ASIR: 130.77, 95% UI: 109.58–150.31) and cirrhosis related to HCV (ASIR: 104.82, 95% UI: 87.05–123.93; $p < 0.001$). In addition, ASIRs (APC: +0.52%, 95% CI: 0.35

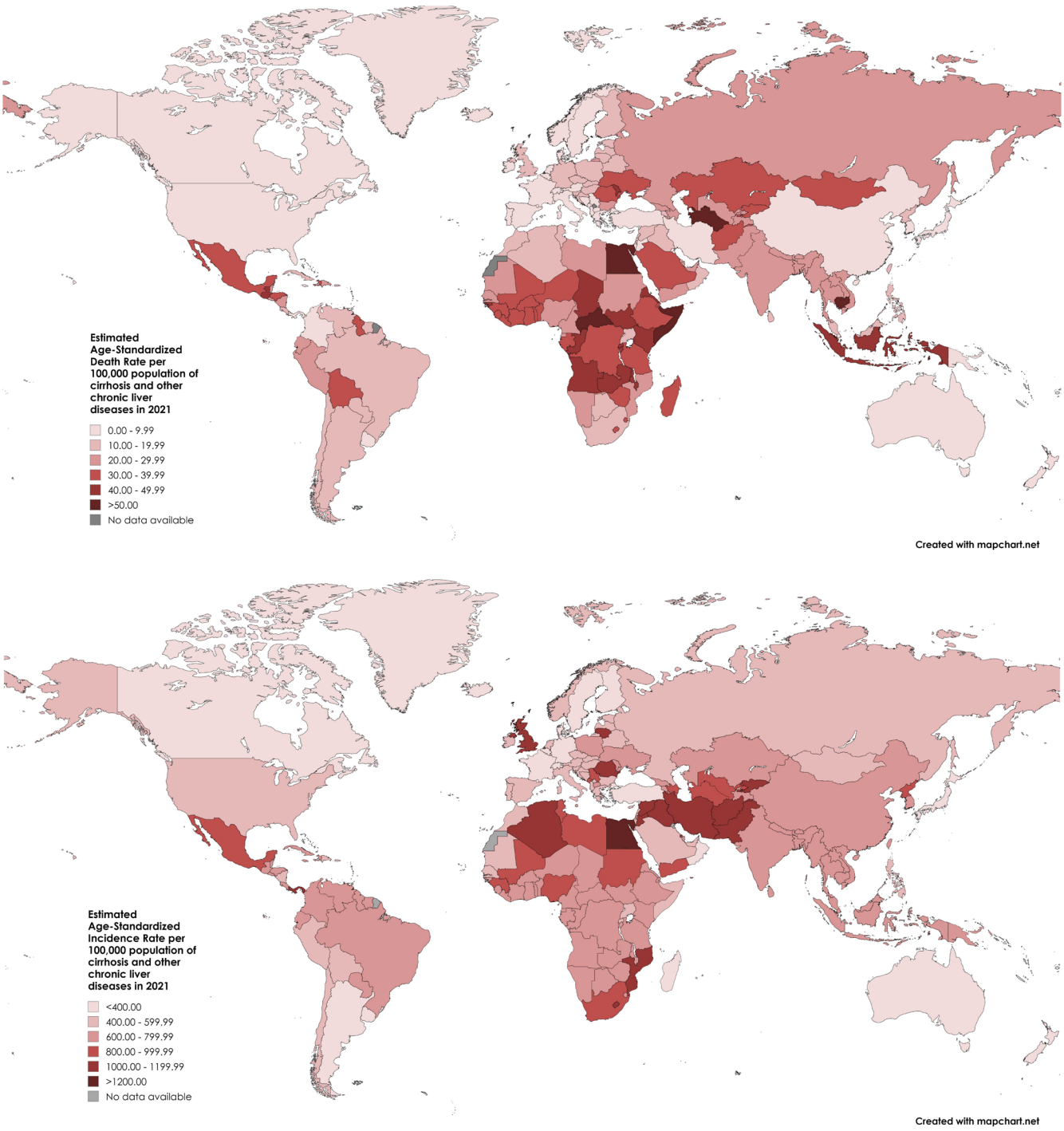

FIGURE 4 | Map depicting the ASIR, ASDR and ASDALY across the countries.

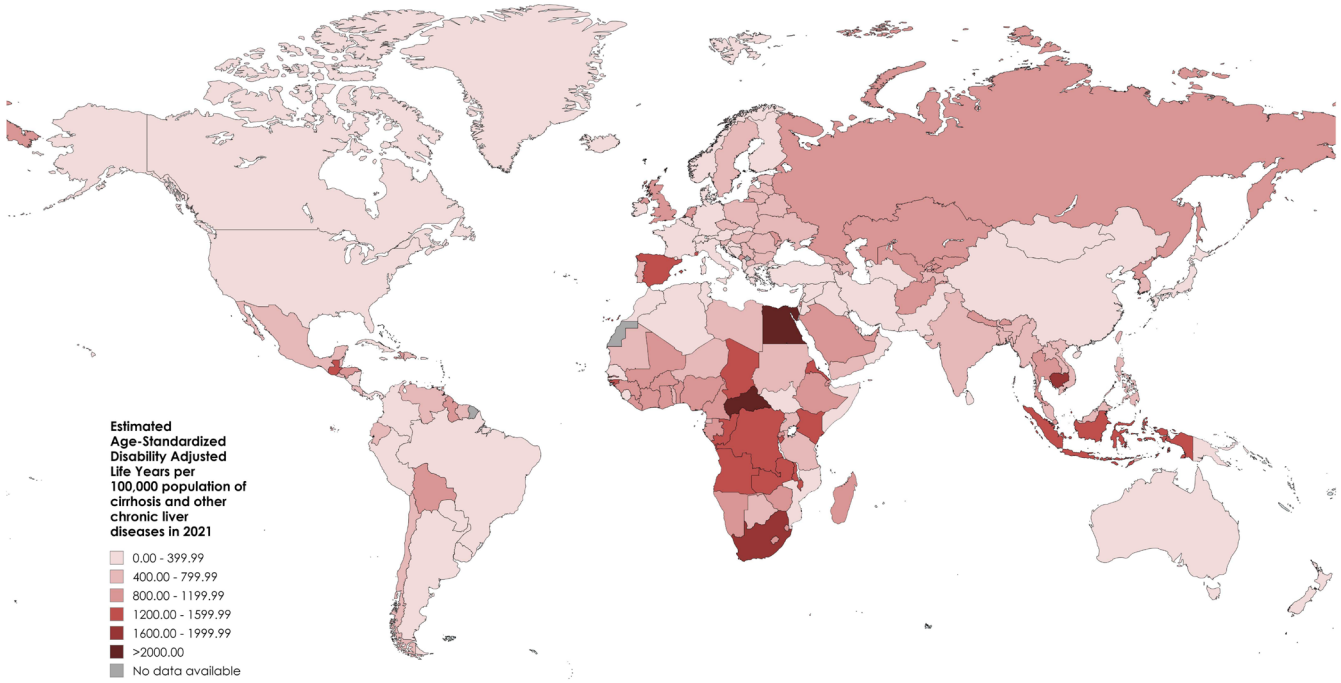

FIGURE 4 | (Continued)

to 0.68; $p < 0.001$) of alcohol-associated cirrhosis in the Americas increased, unlike all other regions where ASIRs remained stable or declined. In the Americas, the ASDR (APC: +1.05, 95% CI: 0.86 to 1.25; $p < 0.001$) and ASDALY (APC: +1.19, 95% CI: 0.97 to 1.41; $p < 0.001$) of MASH-related cirrhosis also increased in contrast to other regions where ASDR and ASDALY remained stable or declined.

In stratified analysis by SDI and aetiology (Figure 7, Supporting Information S12–S14), low SDI regions had the highest ASIR (116.33, 95% UI: 97.56–134.49), ASDR (10.75 95% UI: 8.8–12.78) and ASDALY (322.71, 95% UI: 264.21–386.61) for cirrhosis related to HBV. Cirrhosis related to HCV followed a similar trend with low SDI regions having the highest ASIR (93.28, 95% UI: 77.38–110.68), ASDR (8.29, 95% UI: 6.82–10.13) and ASDALY (249.30, 95% UI: 203.40–302.86). ASIRs related to MASH increased across all SDI classes, most evidently in the high–middle SDI group (APC: +1.17, 95% CI: 1.11 to 1.224; $p < 0.001$).

4 | Discussion

4.1 | Main Findings

Between 2010 and 2021, there was a substantial increase in incident cases and deaths related to cirrhosis and chronic liver diseases. Age-standardised incidence increased between 2010 and 2021, but age-standardised deaths and DALYs declined during the study period. Cirrhosis related to MASH was the only aetiology with an increasing trend in age-standardised incidence. By contrast, age-standardised incidence rates from all other aetiologies declined, including HBV, HCV and alcohol. However, age-standardised deaths related to all aetiologies of cirrhosis and other chronic liver diseases declined during the study period. Age-standardised deaths and DALYs related to MASH increased in the Americas, unlike all other world regions where they declined or remained stable, which could be due to the rapidly rising obesity rates in the Americas [20, 21]. Collectively, these data suggest that age-standardised death rates from cirrhosis and other chronic liver diseases are declining, but incidence rates are increasing, largely driven by MASH.

The decrease in death rates yet increase in incidence could reflect that despite an increase in cirrhosis and other chronic liver diseases, there have been more efficacious management strategies. This is most evident in the management of its contributing aetiologies such as in HBV and HCV [22]; however, advances in treating the complications of cirrhosis and other chronic liver diseases through pharmacological or procedural techniques may have allowed for improvement in recent years [23].

The decline in the burden of viral hepatitis highlights the effectiveness of vaccinations for HBV, and the impact of DAAs and elimination strategies for HCV [5, 24, 25]. Notably, the region of the Americas, which achieved a HBV third dose vaccination rate of 70% the earliest (2000) [26], presented with the lowest ASIR in both 2010 and 2021, showing the efficacy of vaccination in decreasing the incidence of HBV. However, the effectiveness of DAA in HCV is less clear, with the American and European region not having lower ASDR and ASDALY due to HCV despite having the earliest implementation of DAA in 2013 and 2014, respectively [27]. Despite this progress, the burden remains high in low SDI countries, related to gaps in linkage to care and limited vaccination coverage [5, 28, 29]. Underdiagnosis and undertreatment remain a major issue in viral hepatitis [5, 30], further exacerbated by the COVID-19 pandemic [31]. The burden of alcohol-associated cirrhosis appears to be declining; however, these data require

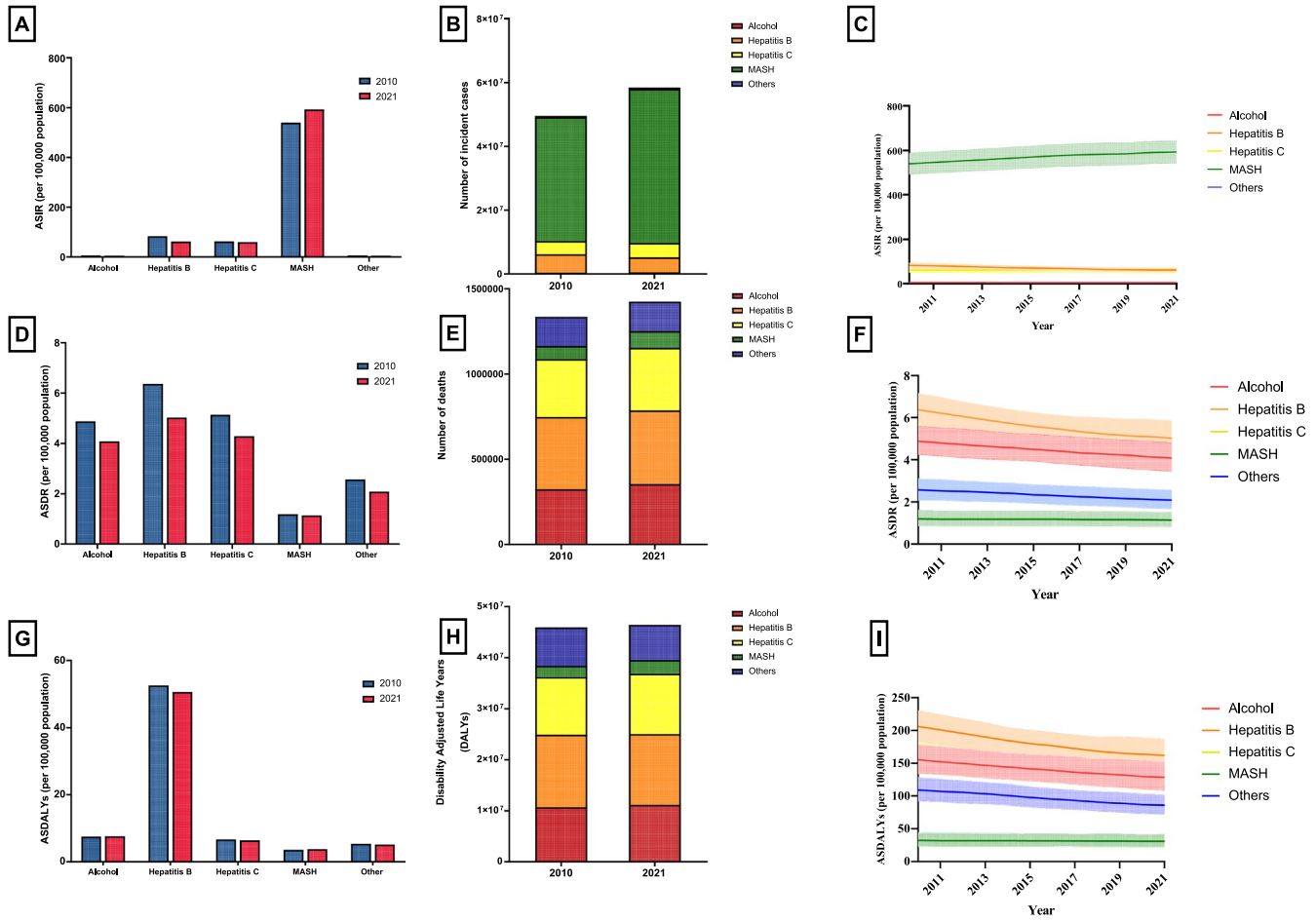

FIGURE 5 | Global incident/age-standardised incident rates, deaths/age-standardised death rates and DALYs/age-standardised DALYs rates of cirrhosis and other chronic liver diseases from 2010 to 2021, stratified by aetiology. (A) Age-standardised incident rates due to cirrhosis and other chronic liver diseases in 2010 and 2021, split by aetiology. (B) Contribution by aetiology of incident cases due to cirrhosis and other chronic liver diseases in 2010 and 2021. (C) Trends in age-standardised incident rates due to cirrhosis and other chronic liver diseases from 2010 to 2021, split by aetiology. (D) Age-standardised death rates due to cirrhosis and other chronic liver diseases in 2010 and 2021, split by aetiology. (E) Contribution by aetiology of deaths due to cirrhosis and other chronic liver diseases in 2010 and 2021. (F) Trends in age-standardised death rates due to cirrhosis and other chronic liver diseases from 2010 to 2021, split by aetiology. (G) Age-standardized DALYs due to cirrhosis and other chronic liver diseases in 2010 and 2021, split by aetiology. (H) Contribution by aetiology of DALYs due to cirrhosis and other chronic liver diseases in 2010 and 2021. (I) Trends in age-standardised DALYs due to cirrhosis and other chronic liver diseases from 2010 to 2021, split by aetiology.

cautious interpretation as underreporting is likely. However, the rapidly rising age-adjusted incidence of cirrhosis related to MASH is sobering and calls for renewed focus to combat the metabolic risk factors contributing to this widespread disease [32].

In recent years, namely from 2018 to 2021, there has also been a slight increase in the APC in ASIR, ASDR and ASDALY. This could be attributed to the COVID-19 pandemic, which saw a rise in obesity [33, 34] and possibly alcohol consumption [35]. In addition, concurrent COVID-19 and cirrhosis or chronic liver disease were also associated with higher mortality, especially in unvaccinated individuals [36, 37], possibly resulting in an increase in ASDR.

4.2 | In Context With Current Literature

This study builds on previous analyses of the burden of cirrhosis and other chronic liver diseases using GBD 2017 and GBD 2019 data, providing a comprehensive analysis of the global and regional burden of cirrhosis and other chronic liver diseases and its aetiologies [3, 16, 38]. Compared to previous GBD studies, GBD 2021 includes estimates for COVID-19 and OPRMs, offering relevant and up-to-date insights into potential changes in trends due to the pandemic. The overall trends in cirrhosis and other chronic liver diseases and the contribution of various aetiologies in this study are supported by other country or region-specific studies [39–41]. A previous study focused on liver-related complications from MASLD from 1990 to 2021 [42]. The current study builds upon this by providing data for incidence, mortality and DALYs from the major aetiologies of liver disease from 2010 to 2021.

4.3 | Limitations

The limitations of this study largely depend on the quality and validity of the data provided by GBD 2021. Data

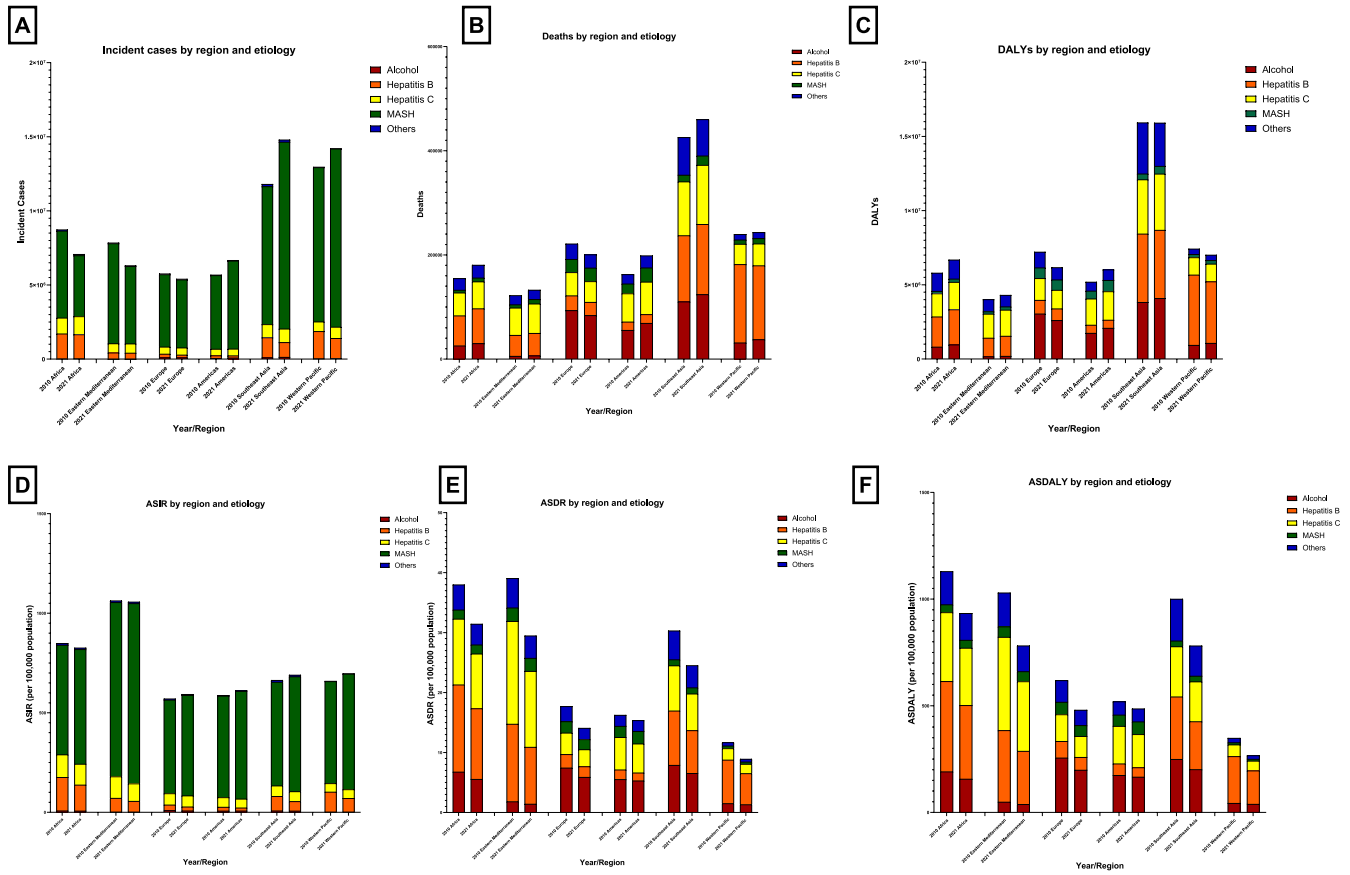

FIGURE 6 | Contribution of aetiologies stratified by the WHO region. (A) Contributions of aetiologies to the incident cases for cirrhosis and chronic liver diseases, stratified by the WHO region. (B) Contributions of aetiologies to the deaths for cirrhosis and chronic liver diseases, stratified by the WHO region. (C) Contributions of aetiologies to the DALYs for cirrhosis and chronic liver diseases, stratified by the WHO region. (D) Contributions of aetiologies to the ASIR for cirrhosis and chronic liver diseases, stratified by the WHO region. (E) Contributions of aetiologies to the ASDR for cirrhosis and chronic liver diseases, stratified by the WHO region. (F) Contributions of aetiologies to the ASDALY for cirrhosis and chronic liver diseases, stratified by the WHO region.

standardisation and estimate methods were used to account for missing data [12], which introduces uncertainty and variability. This was particularly evident in low SDI countries [19], which have increasingly contributed to the global burden of alcohol and MASH in the recent decades [43, 44]. Furthermore, low and middle SDI countries might have large health gaps as a result of a lack of well-functioning health information systems [45], resulting in inaccurate estimates. Underreporting of alcohol consumption could also contribute to lower estimates. People with multiple aetiologies of liver disease were not accounted for in the GBD 2021 study. In addition, the GBD study did not distinguish between liver-related deaths versus non-liver related deaths; hence, these data require cautious interpretation.

4.4 | Implications for Clinical Care and Research

Despite a decline in age-adjusted death rates, the burden of cirrhosis remains high. These data have important implications for healthcare policymakers and public health specialists. National policies and health promotion initiatives aimed at preventing cirrhosis, such as by targeting the metabolic risk factors of MASH, are lacking [46, 47]. Increasing access to therapies for MASH, such as resmetirom, may alleviate the burden of MASH while awaiting more effective therapies [48, 49]. Despite the decline in the burden of cirrhosis related to HBV and HCV, its burden remains enormous, calling for renewed efforts towards eliminating viral hepatitis. Improving vaccination coverage, screening and linkage to care, especially in lower SDI countries, is likely to further reduce the burden of viral hepatitis [50–53]. Public health policies directed against heavy alcohol use [54] may further reduce the burden of alcohol-associated liver disease [55, 56].

In conclusion, death rates from cirrhosis are declining. However, the overall incidence is increasing, driven by MASH. Age-standardised deaths and DALYs related to MASH increased in the Americas, unlike all other world regions where they declined or remained stable. Concerted efforts targeted at the metabolic risk factors to curb the rising incidence of MASH, increasing linkage to care for viral hepatitis and reducing heavy alcohol consumption are required to sustain the decline in the global burden of cirrhosis.

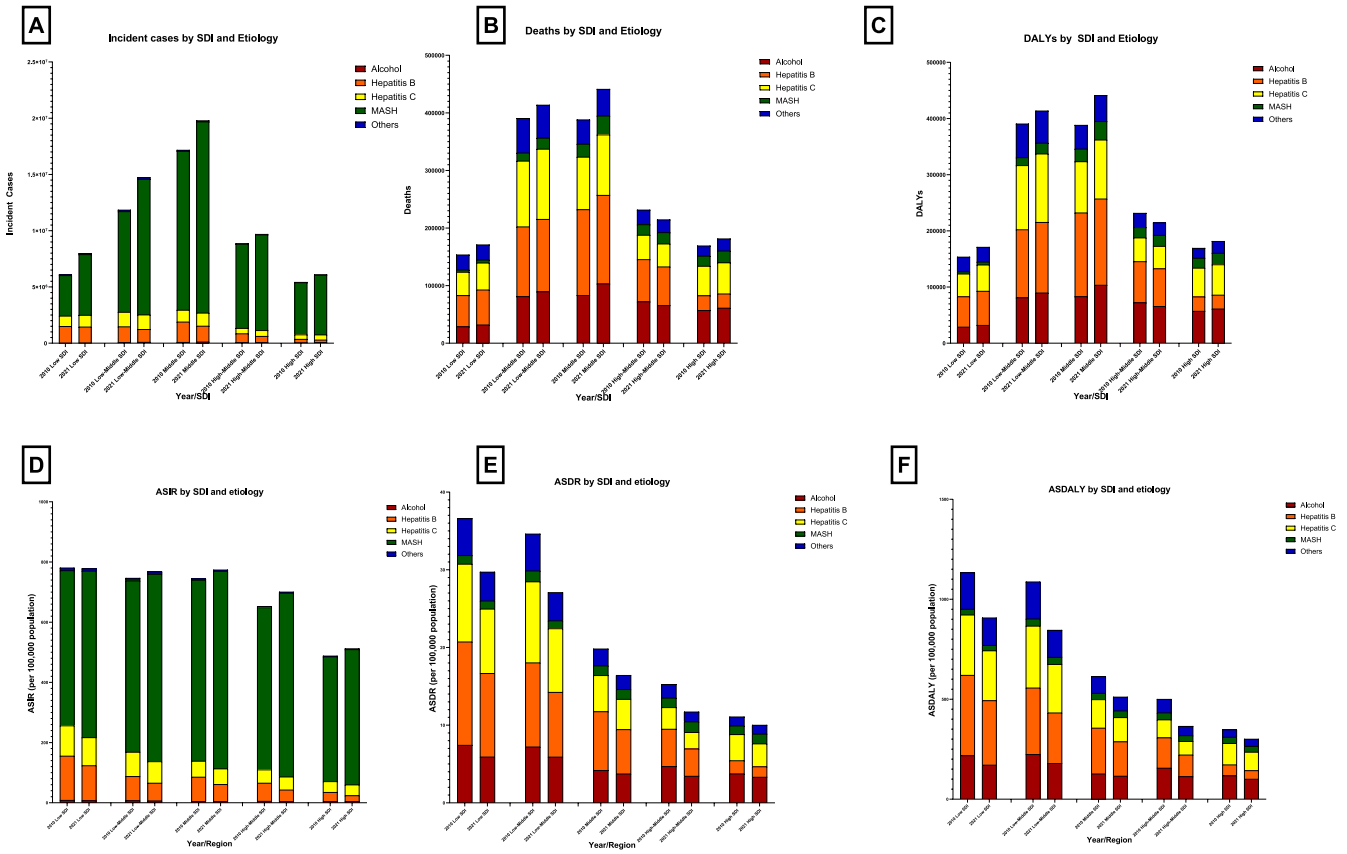

FIGURE 7 | Contribution of aetiologies stratified by SDI. (A) Contributions of aetiologies to the incident cases for cirrhosis and chronic liver diseases, stratified by SDI. (B) Contributions of aetiologies to the deaths for cirrhosis and chronic liver diseases, stratified by SDI. (C) Contributions of aetiologies to the DALYs for cirrhosis and chronic liver diseases, stratified by SDI. (D) Contributions of aetiologies to the ASIR for cirrhosis and chronic liver diseases, stratified by SDI. (E) Contributions of aetiologies to the ASDR for cirrhosis and chronic liver diseases, stratified by SDI. (F) Contributions of aetiologies to the ASDALY for cirrhosis and chronic liver diseases, stratified by SDI.

Author Contributions

All authors approve the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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All authors have made substantial contributions to all of the following: (1) the conception and design of the study, acquisition of data or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content and (3) final approval of the version to be submitted. No writing assistance was obtained in the preparation of the manuscript. The manuscript, including related data, figures and tables, has not been previously published and the manuscript is not under consideration elsewhere.

Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki. The study was exempt from IRB review as no confidential patient information was involved.

Conflicts of Interest

C.H.N. has served as a consultant for Boxer Capital. R.L. serves as a consultant to Aardvark Therapeutics, Altimmune, Anylam/Regeneron, Amgen, Arrowhead Pharmaceuticals, AstraZeneca, Bristol-Myer Squibb, CohBar, Eli Lilly, Galmed, Gilead, Glympse Bio, Hightide, Inipharma, Intercept, Inventiva, Ionis, Janssen Inc., Madrigal, Metacrine Inc., NGM Biopharmaceuticals, Novartis, Novo Nordisk, Merck, Pfizer, Sagimet, Theratechnologies, 89 bio, Terns Pharmaceuticals and Viking Therapeutics. In addition, his institutions received research grants from Arrowhead Pharmaceuticals, Astrazeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, Galectin Therapeutics, Galmed Pharmaceuticals, Gilead, Intercept, Hanmi, Intercept, Inventiva, Ionis, Janssen, Madrigal Pharmaceuticals, Merck, NGM Biopharmaceuticals, Novo Nordisk, Merck, Pfizer, Sonic Incytes and Terns Pharmaceuticals. D.H., co-founder of LipoNexus Inc., has served as an advisory board member for Gilead. All other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability Statement

No dataset was used in this study. All articles in this manuscript are publicly available from Medline and Embase.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.