Hepatitis B and C mortality from 1990 to 2019 in China: a Bayesian age-period-cohort analysis

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Background: Significant decreases in hepatitis B virus (HBV) and hepatitis C virus (HCV) infections have been observed in China, but both remain leading public health challenges. Estimating the components and trends in HBV and HCV mortality is vital for disease control planning. The current analysis investigated time trends in hepatitis B and C mortality and the relationships with age, period, and birth cohort from 1990 to 2019. We also made projections for 2030–2034 in China.

Methods: Mortality data related to hepatitis B and C were obtained from the Global Burden of Disease (GBD) study, which was stratified by complications, age, sex, and specific geographical locations. An age-period-cohort (APC) analytical framework was adopted to measure age, period, and cohort effects, which fits a log-linear Poisson model over a Lexis diagram of observed rates and quantifies the additive effects of age, period, and birth cohorts. We estimated longitudinal age curves (expected longitudinal age-specific rates), net drift (overall annual percentage change), local drift (annual percentage change in each age group), period, and cohort relative risks. A Bayesian APC analysis was used to project future age-specific hepatitis B and C deaths.

Results: In China, the age-standardized mortality rate (ASMR) of hepatitis B and C decreased by 67% and 58% from 1990 to 2019, respectively. The overall annual percentage changes in hepatitis B and C were −4.97% and −6.49% for males and −3.85% and −6.09% for females, respectively. After adjusting for period and cohort effects, we observed an exponential increase in hepatitis C mortality with age, with the Bell-like curves peaking at approximately 50 years old for hepatitis B. The Bayesian APC analysis projected that hepatitis B and C deaths would decrease dramatically by 42% and 22% for the periods 2016–2019 and 2030–2034, respectively. The declines in ASMRs related to hepatitis B and C were associated with the improvements in the Chinese Socio-Demographic Index.

Conclusions: Although the burden of hepatitis B and C mortality is likely to continue declining in China, the hepatitis B and C mortality was still high. Therefore, the national efforts should still be strengthened to achieve the global hepatitis elimination targets.

Keywords: Hepatitis B; hepatitis C; mortality; age-period-cohort; trends

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Introduction

The hepatitis B virus (HBV) and hepatitis C virus (HCV) remain major global health issues. The World Health Organization (WHO) estimated that 296 million people were living with chronic hepatitis B infection, and 58 million had chronic hepatitis C infection worldwide, representing 4.4% of the world population in 2019 (1,2). Both HBV and HCV are leading causes of chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC) and have resulted in an estimated 1.57 million deaths in 2019, accounting for 2.1% of all deaths worldwide (1). In 2016, the WHO set a commitment to eliminating HBV and HCV by the year 2030 via a series of therapeutic measures (3,4). The coverage targets in 2030 for HBV and HCV are a 90% reduction in incidence and a 65% reduction in mortality related to chronic HBV and HCV infections. In the past two decades in China, HBV infections have declined or remained stable, and HCV infections have shown a significant increase (5). However, with 78 million HBV and 8 million HCV chronic carriers, HBV and HCV infections remain two of China's leading public health challenges (6,7).

Estimating the components and trends in HBV and HCV mortality is vital for HBV and HCV control planning. For the entire Chinese population, accurate information regarding the mortality trends related to hepatitis B and C is scarce. One recent study reported the 30-year trends of incidence and mortality of hepatitis B and C in China (8). However, there were still some gaps in this study for the detailed analyses of mortality trends, such as the mortality related to cirrhosis. Without accurate data, it is impossible to identify and comprehensively decrease the burden associated with hepatitis B and C. This study adopted an age-period-cohort (APC) analysis to examine China's current and future HBV and HCV mortality rates, which have been adopted in descriptive epidemiology for certain chronic diseases (9-11). We hope our findings can refine our knowledge of the mortality trends of HBV and HCV in China and recognize potential risk factors for the changes in HBV and HCV mortality. In turn, this may help guide public health policy, resource allocation, and the design of intervention programs. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5676/rc).

Highlight box

Key findings

- The burden of hepatitis B and C mortality is likely to continue declining in China, the hepatitis B and C mortality was still high.

What is known and what is new?

- Significant decreases in hepatitis B and C infections have been observed in China, but both remain leading public health challenges.
- The current analysis investigated time trends in hepatitis B and C mortality and the relationships with age, period, and birth cohort from 1990 to 2019. We also made projections for 2030–2034 in China.

What is the implication, and what should change now?

- The national efforts should still be strengthened to achieve the global hepatitis elimination targets.

Methods

Data

All anonymized mortality data associated with HBV and HCV infections from 1990–2019 in China were collected from the Institute for Health Metrics and Evaluation's most recent Global Burden of Disease database (GBD 2019) (publicly accessed online) (12). The GBD 2019 aims to quantify the comparative magnitude of health loss due to diseases, injuries, and risk factors by age, sex, and specific geographical locations. The GBD 2019 synthesizes a large number of input sources to estimate mortality, including population-based serosurveys, claims and hospital discharges, cancer registries, vital registration systems, and published case series. The GBD 2019 used the Cause of Death Ensemble modelling model to estimate mortality due to cirrhosis, liver cancer, and acute hepatitis. Detailed descriptions of the overall GBD methodology have been published previously (13). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Because this study does not contain personal or medical information about any identifiable living individuals, and animal subjects were not involved, the ethics approval and informed consent was waived by the Institutional Review Board of our hospital.

The specific causes of death related to hepatitis B and C were classified into six categories: acute hepatitis due to hepatitis B, cirrhosis and other chronic liver diseases due to hepatitis B, liver cancer due to hepatitis B, acute hepatitis due to hepatitis C, cirrhosis and other chronic liver diseases due to hepatitis C, and liver cancer due to hepatitis C, all of which were mutually exclusive. The three specific death causes due to hepatitis B and hepatitis C were grouped as the total burden related to hepatitis B and the total burden related to hepatitis C.

The Socio-Demographic Index (SDI), expressed on a score from 0 (minimum level of development) to 1 (maximum level of development), is a summary measure that identifies where GBD locations sit on the spectrum of socioeconomic development (14). The SDI is calculated based on the average educational attainment in the population aged 15 years or older, total fertility rate under 25 years, and lag-distributed income per capita. The cut-off values used to determine the SDI quintiles were computed using estimates from countries with populations over 1 million. More details regarding the calculation of the SDI are reported in previous GBD publications (15).

Statistical analyses

The data collected from the GBD 2019 included the death count, mortality rate, and the age-standardized mortality rate (ASMR) per 100,000 population by age, sex, and complications, which was used to depict and analyze trends in the disease burden related to hepatitis B and C from 1990 to 2019. The ASMR is standardized to the GBD 2019 global age-standard population. The calculation formula for ASMR was as follows:

$$\text{ASMR} = \frac{\sum Age\ composition\ of\ standard\ group\ population \times Age\ specific\ mortality}{Age\ composition\ of\ standard\ population} \quad [1]$$

We also tested the association between the SDI and ASMR related to hepatitis B and C by year. The detailed analytical methods used for this study have been reported previously (1,16,17), and the related codes can be accessed at http://ghdx.healthdata.org/gbd-2019/code.

When measuring mortality, standard statistical analysis is insufficient to decompose the death and health risks. The age-period-cohort (APC) model estimates the cumulative health risks for the past birth cohort and shows the mortality risk for the population within each period (18). Hepatitis B and C infections are strongly associated with a region's economic level and health status. Moreover, age is a key risk factor, affecting both health behavior and disease course. The APC analytical framework can decompose time trends and afford relatively efficient estimation results. As the birth cohort was measured by adopting the calculation formula: birth cohort = period − age, the association between them would be ideally linear. This challenge could be avoided by generating measurable APC parameters and functions without imposing arbitrary constraints on the model parameters (19).

By adopting the APC analytical framework, we estimated the longitudinal age curves, the local and net drifts, and period (or cohort) rate ratios (RR) (19). For the age effect, the net and local drifts represented the overall annual percentage change and the annual percentage change of the expected age-specific rates, respectively. The expected age-specific rates adjusted for period effects in the control cohort were indicated by the longitudinal age curve. The ratio of age-specific rates in each period (or cohort) compared with the control one were indicated by the period (or cohort) RR, which reflected time effects. The period effect can be influenced by health factors and historical events, and cohort effects influenced by unequal exposure levels or uneven population exposure in diverse age subgroup at a critical development period.

Based on the GBD 2019 global age-standard population, the mortality rates were shown as age-standardized. The mortality and population data were arranged into consecutive 5-year periods from 1990 to 2019 and successive 5-year age intervals from under 5 years to 95+. In this analysis, the birth cohort was defined by the difference between the medium value of the age interval and the period interval. We took the birth cohort of 1960–1964 (median, 1962) as the control group because they may have a high risk of liver complications. The period 2010 to 2014 (median 2012) was used as the control period because WHO's elimination goal for viral hepatitis was declared in 2016. The Wald chi-square test was adopted to test the notable significance of the estimable parameters. This analysis assumed all statistical tests were 2-tailed, and P<0.05 was deemed significant. A reported APC Web Tool was adopted for the parameter estimation along with associated statistical hypothesis tests, whose codes can be found on GitHub (https://github.com/CBIIT/nci-webtools-dceg-age-period-cohort). The functions used in the analysis are as follows (18,19):

Longitudinally, the expected rate per 100,000 population among persons born in year *c* and followed up at age *a*:

$$R(a \mid c) = \text{LongAge}(a \mid c_0) \times CRR(c \mid c_0) \times e^{PD(c+a)} \quad [2]$$

LongAge is the fitted longitudinal age-specific rates in the control cohort c_0 adjusted for period deviations. CRR is cohort rate ratios, and PD is period deviations.

Cross-sectionally, the expected rates by age conditional

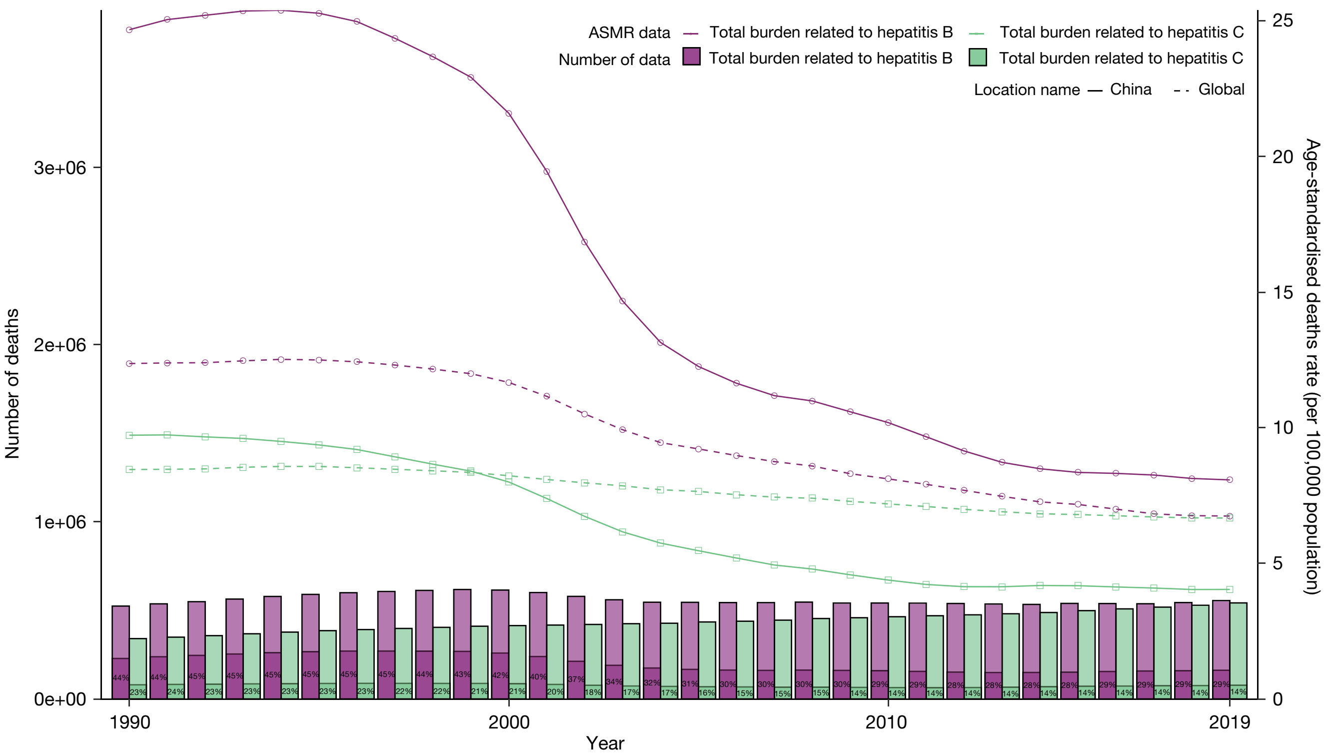

Figure 1 Counts and age-standardized mortality rates (ASMR) for both sexes caused by hepatitis B and C from 1990 to 2019 in China and globally. The bars with light purple and green indicate the number of deaths globally, and the bars with deep purple and green indicate the number of deaths in China, respectively, where the percent data is China's proportion in the global levels. The solid lines indicate the ASMR globally, and the dashed lines indicate the ASMR in China.

on period p:

$$R(a \mid p) = \text{CrossAge}(a \mid p_0) \times PRR(p \mid p_0) \times e^{CD(p\text{-}a)} \qquad [3]$$

CrossAge is the fitted cross-sectional age-specific rates in the control period p0 adjusted for cohort deviations. PRR is period rate ratios, and CD is cohort deviations.

Expected rates by period conditional on age a:

$$R(p \mid a) = \text{FTT}(p \mid a_0) \times \frac{\text{CrossAge}(a \mid p_0)}{\text{CrossAge}(a_0 \mid p_0)} \times e^{PD(c+a)} \qquad [4]$$

FTT is the fitted rates in the control age group a_0 adjusted for cohort deviations.

A Bayesian age-period-cohort analysis was adopted for projecting the future age-specific number of deaths related to hepatitis B and C from 2020 to 2034 (9,10). This timeframe was chosen because the risk of complications related to hepatitis B and C, such as HCC, would notably increase in the next 15 years after the infection was established (20). By assuming the age, period, and cohort effects are similar in the adjacent time, the second-order random walk was adopted in the Bayesian APC model for smoothing priors of the effects of age, period and cohort to predict posterior mortality. This approach combined nested Laplace approximations, which showed more favorable coverage and precision than other methods by averting any mixing and convergence issues due to the sampling techniques associated with Markov Chain Monte Carlo. The Bayesian APC analysis was carried out by adopting R-package BAPC (version 0.0.34).

Results

Overall trends in mortality

Figure 1 shows the trends in hepatitis B and C mortality. In China, the annual total deaths from hepatitis B notably decreased from 0.229 to 0.162 million from 1990 to 2019, respectively. The proportion reported globally decreased considerably from 44% in 1990 to 29% in 2019. The ASMR of hepatitis B in China declined from 24.67 in 1990 to 8.07 per 100,000 (a decrease of 67%) in 2019, although it is still slightly higher than the global level in 2019 (6.74 per 100,000). The annual total deaths from hepatitis C in China decreased from 0.079 to 0.078 million from 1990 to 2019. However, due to the increased number of global deaths caused by hepatitis C, the proportion for China in the GBD decreased significantly from 23% in 1990 to 14% in 2019. The ASMR of hepatitis C in China declined from 9.72 in 1990 to 4.03 per 100,000 (a decrease of 58%) in 2019, which is notably lower than the global level since 2000.

ASMR related to gender, cause, and age

Figure 2 shows the trends of ASMR stratified by gender. For hepatitis B, the overall rates for ASMR in males and females declined from 38.72 to 13.75 per 100,000 population (a decrease of 64%) and from 11.83 to 2.86 per 100,000 (a decrease of 76%) in China, respectively. For specific complications, the sex-specific ASMR attributed to hepatitis B declined by 84% and 90% in acute hepatitis, 66% and 68% in cirrhosis and other chronic liver diseases, and 62% and 73% in liver cancer for males and females, respectively. For hepatitis C, the ASMR rates for males and females in China declined from 10.99 to 5.49 per 100,000 population (a decrease of 50%) and from 8.41 to 2.80 per 100,000 (a decrease of 67%), respectively. For specific complications, the sex-specific ASMR attributed to hepatitis C declined by 94% and 97% in acute hepatitis, 44% and 62% in cirrhosis and other chronic liver diseases, and 58% and 68% in liver cancer for males and females, respectively.

There were substantial differences in the ASMRs attributed to hepatitis B and C across age groups and sex (*Figure 3*). In 2019, the highest ASMR of hepatitis B in males was more than 15,000 deaths per 100,000 population in ages 50–69 years, and the highest ASMR in females was over 3,500 deaths in ages 60–69 years. The ASMRs of hepatitis C in males and females mainly occurred in the 45–84 and over 55 age groups, respectively, with more than 4,000 and 2,000 deaths per 100,000 population. Compared with 1990, the ASMRs of hepatitis B in 2019 declined in almost all age groups except the older population, decreasing from 7% in males aged 65–69 to 96% in females aged 0–9 years. For hepatitis C, the ASMRs in 2019 mainly declined in the younger female population, decreasing from 7% in males aged 55–59 to 99% in females aged 0–9. However, the ASMRs of hepatitis B increased in the older populations aged 80+ in both males and females. The ASMRs of hepatitis C began to increase in males from 50+ years, from 6% at 50–54 years to 241% at 85+ years and increased only in females from 80+ years.

Impact of the SDI on ASMR

Figure 4 shows the changes in ASMR across the SDI from 1990 to 2019. With improvements in the SDI, a decline in ASMRs related to hepatitis B and C was exhibited in China.

Age-period-cohort analysis on ASMR

In hepatitis B and C, the net drifts were −4.97% [95% confidence interval (CI): −5.21% to −4.72%] and −3.85% (95% CI: −4.30% to −3.40%) for males, respectively, and −6.49% (95% CI: −6.82% to −6.12%) and −6.09% (95% CI: −6.58% to −5.60%) for females, respectively (*Figure 5*). The values of local drifts lay predominantly below 0 for almost all age groups in males and females, suggesting ameliorations in decreasing hepatitis B and C mortality.

The risk of death from hepatitis B for both sexes showed Bell-like curves (*Figure 6*). Under 50 years, an increase with age was observed and gradually decreased thereafter. For hepatitis C, the risk of death accelerated with age, especially in males. By adjusting for age and birth cohort, declined period relative risks were observed for both sexes (*Figure 6*). However, a more rapidly declining trend was found for females than males during the entire study period. Similar patterns of cohort relative risks were also observed for both sexes, which began to decrease after 1900 and decreased more quickly for females (*Figure 6*). These net drifts, local drifts, cohort, and period effects were all notably significant ($P<0.05$).

Mortality projection

A Bayesian APC analysis was performed to project future mortality trends for hepatitis B and C. The total number of deaths from hepatitis B was observed to continue to decrease substantially, from 157,842 deaths per year in the period 2016–2019 to 91,895 deaths per year in the period 2030–2034. A moderate reduction in the total number of deaths from hepatitis C would be observed, from 74,405 deaths per year in the period 2016–2019 to 57,845 deaths per year in the period 2030–2034. However, there were notable differences in the distribution of hepatitis B and C

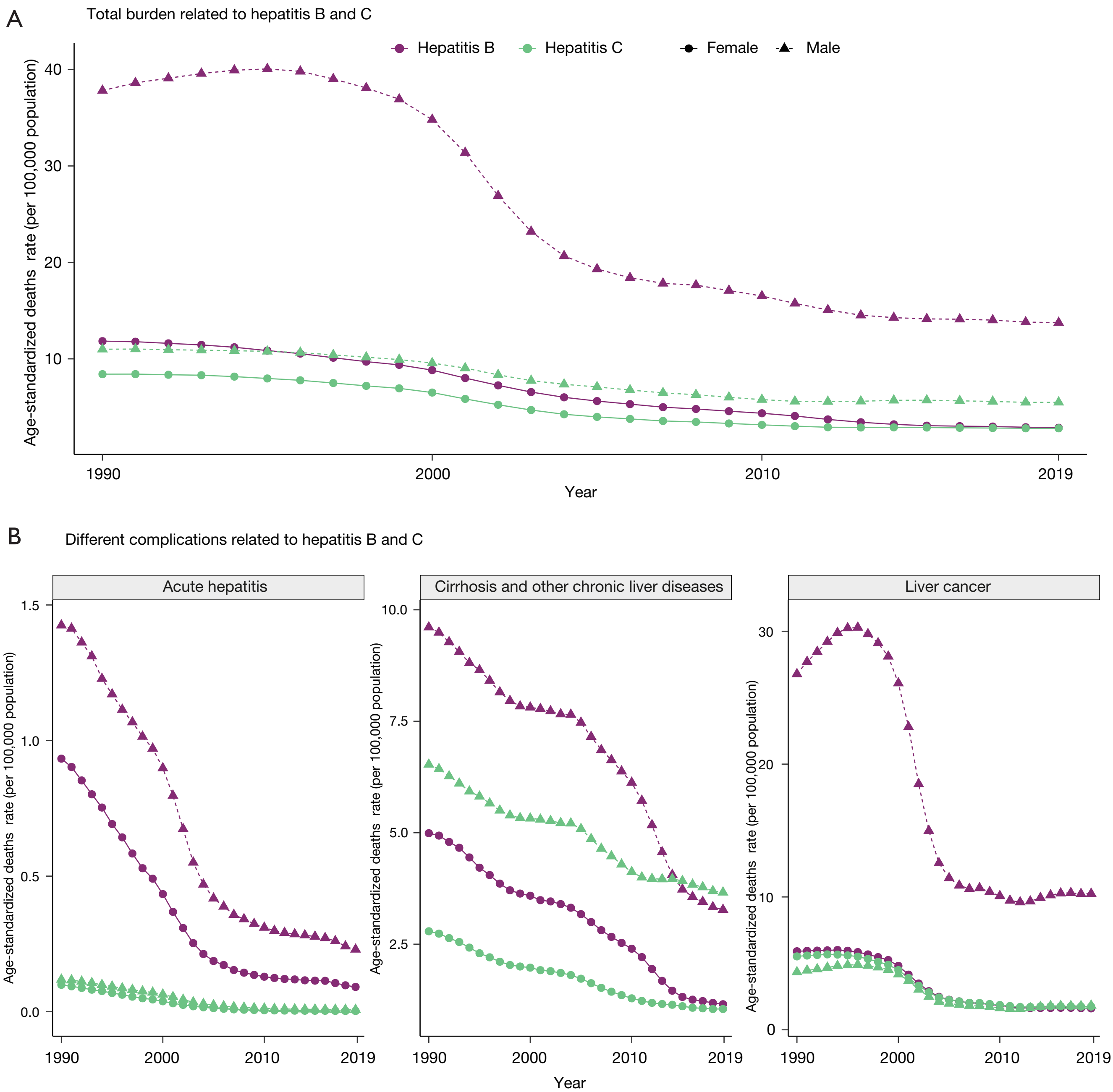

Figure 2 Age-standardized mortality rates resulting from hepatitis B and C in China from 1990 to 2019 stratified by sex and cause. (A) Total burden related to hepatitis B and C. (B) Acute hepatitis, cirrhosis and other liver diseases, and liver cancer caused by hepatitis B and C.

deaths across age groups (*Figure 7*), with more occurring in the younger age groups (under 50 years).

Discussion

Our study investigated the long-term trends in hepatitis B and C mortality from 1990 to 2019 in China. The ASMR per 100,000 Chinese population decreased more substantially compared to global trends, especially in the younger population with hepatitis B. The ASMR in hepatitis B is not significantly different from the global level, and hepatitis C has become notably lower. This

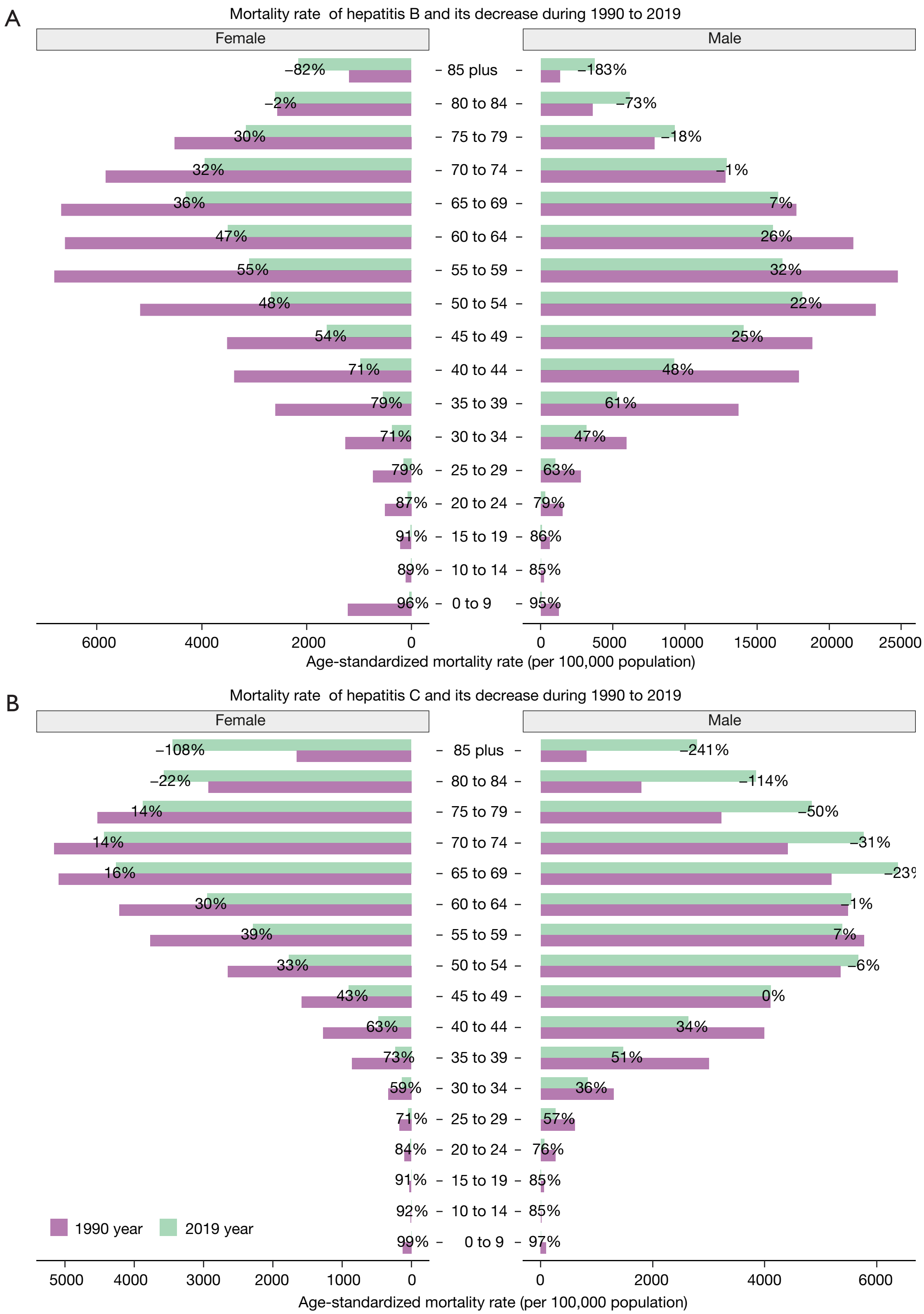

Figure 3 Chinese age-standardized mortality rates resulting from hepatitis B and C and the changes between 1990 and 2019 stratified by age and gender.

finding may be due to national efforts, such as the routine immunization policy for hepatitis B prevention and the 'test and treat all based on needs and demand' strategy for hepatitis C (21,22). This health transition is predictably linear with the SDI improvement. There may be important lessons from China for other countries in the Asia-Pacific region where elimination targets remain unmet (23).

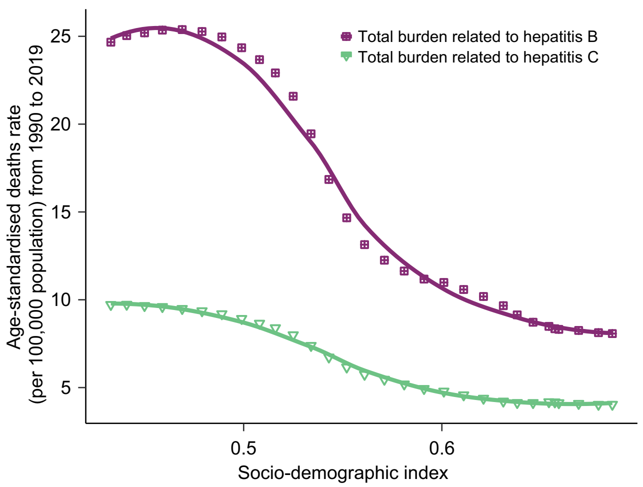

Figure 4 The age-standardized mortality rates (ASMR) of hepatitis B and C in China by Socio-Demographic Index, 1990–2019. Points from left to right depict estimates from each year from 1990 to 2019.

Although the mortality rate substantially decreased in both males and females, the ASMR of hepatitis B and C mortality in males remained almost four and two times greater than in females, respectively, from 1990 to 2019. The main drivers of the ASMRs were liver cancer and cirrhosis, especially complications due to hepatitis B. Liver cancer is predominant among men, with the highest male-to-female ratios in areas of high incidence (20). One recent study also found that the male-to-female ratio for age-standardized liver cancer mortality was 2.8 (24). Male habits, such as drinking alcohol, may cause these gender effects (25). These findings indicate that reducing the disease burden related to hepatitis B and C in males should continue to be pursued.

In the age-period-cohort analyses, a declining trend was found in both cohort and period effects for hepatitis B and C mortality in China, suggesting successful national policies (21,22). We estimated that hepatitis B and C deaths would decrease dramatically by 42% and 22% from 2016–2019

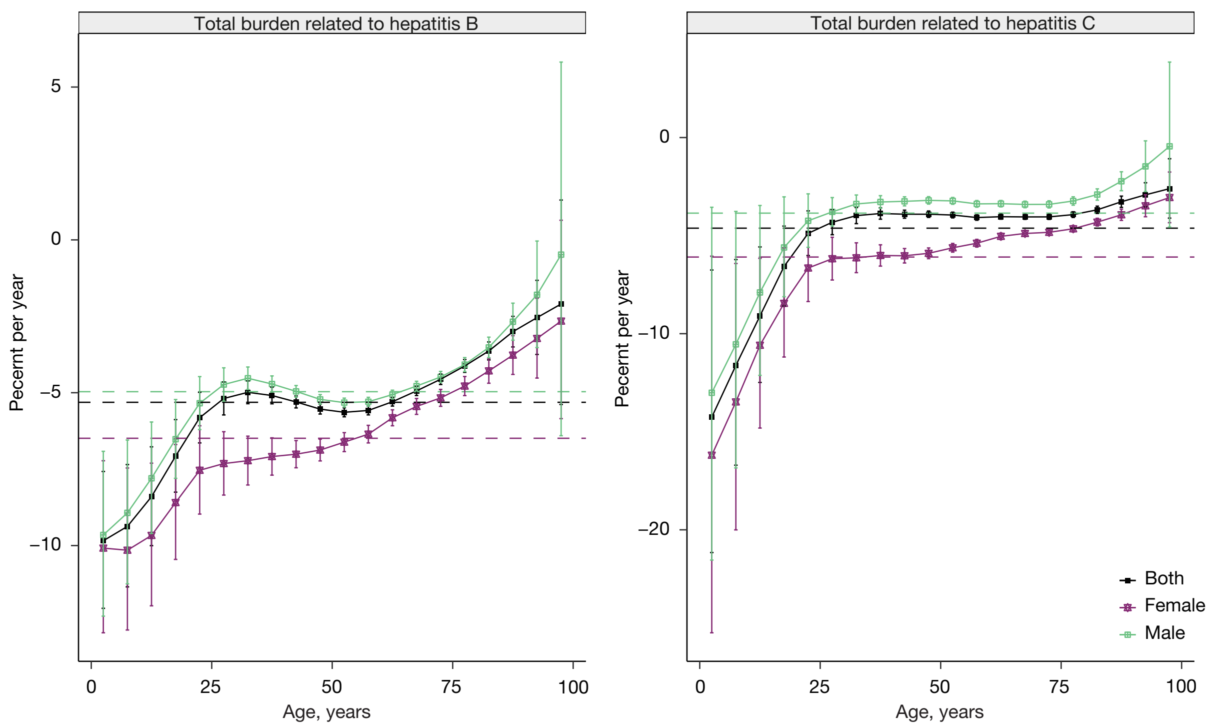

Figure 5 Local drifts with net drift values for hepatitis B and C mortality in China during 1990 and 2019. The horizontal dashed lines are the net drifts, and the solid lines of the curve are the local drifts.

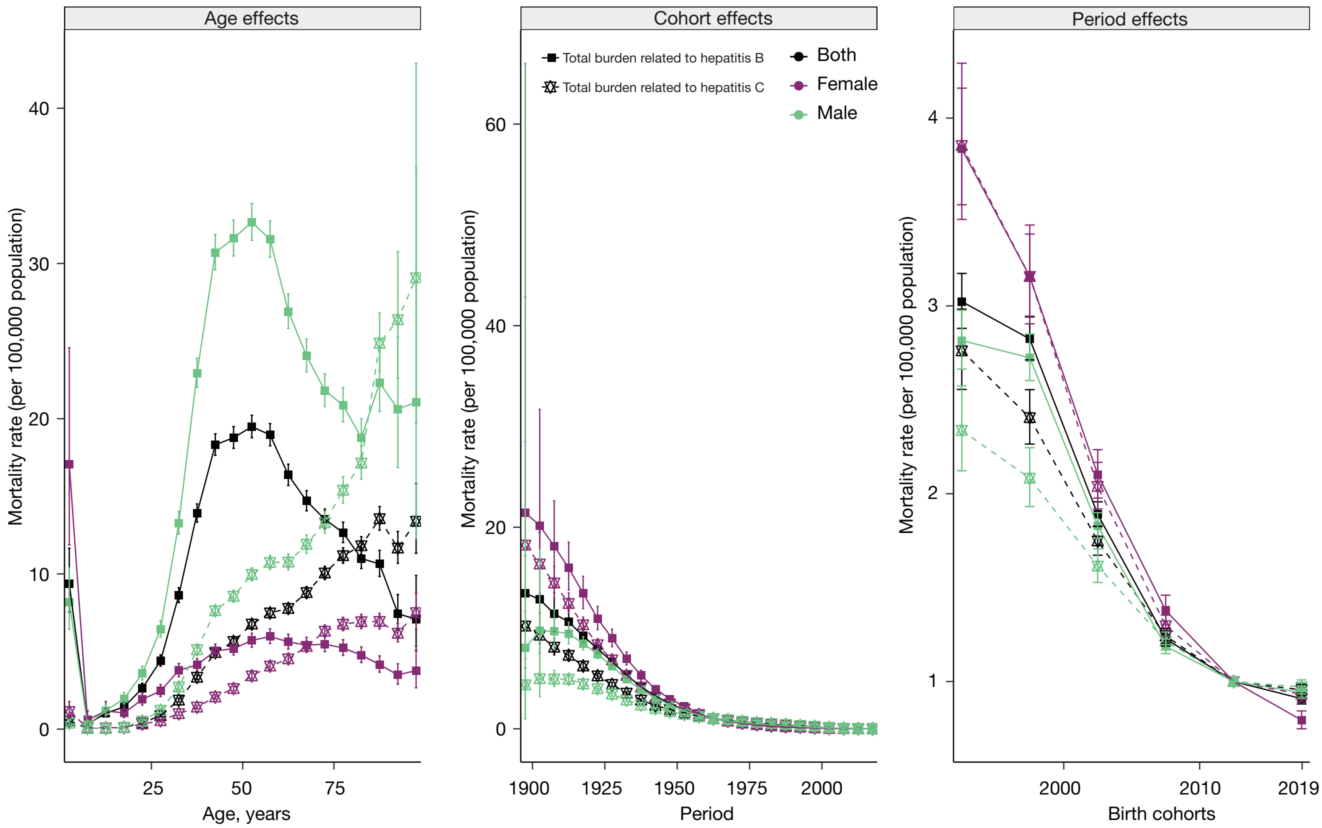

Figure 6 Parameter estimates of age, period, and cohort effects on hepatitis B and C mortality rates in China from 1990 to 2019. Age effects show the fitted longitudinal age curves of hepatitis B and C mortality (per 100,000 person-years) and the corresponding 95% CIs (some were too narrow to show). Cohort effects show the relative risk of each cohort compared with the control (cohort 1960–1964) adjusted for age and nonlinear period effects and the corresponding 95% CI. Period effects show the relative risk of each period compared with the control (2010–2019) adjusted for age and nonlinear cohort effects and the corresponding 95% CI.

and 2030–2034, respectively. To achieve the coverage targets of a 65% reduction in hepatitis B and C mortality in 2030 (3,4), more national efforts, such as universal screening for hepatitis B and C infections (7), should be implemented in China. This finding was also consistent with a Japanese study, which found the challenges in controlling hepatitis remain, although the disease burden associated with hepatitis B and C is expected to decrease by 2035 (26).

Our study showed a peak in the 2019 ASMRs related to hepatitis B and C in the 50–65 and over 55-year-old groups, respectively. After adjusting for period and cohort effects, we further quantitatively determined an exponential increase in hepatitis C mortality with age, and the Bell-like curves peaked around 50 years old for hepatitis B. This divergent phenomenon might be explained by the different transmission routes of hepatitis B and C. Mother-to-child and drug use are the main transmission routes of hepatitis B and C, respectively, which lead to infections occurring in infants for hepatitis B and adults for hepatitis C (27,28). After infection with hepatitis B and C, cirrhosis and liver cancer may develop over a 20- to 30-year period, which might cause increased mortality rates with age for hepatitis C and peak mortality rates at approximately 50 years old for hepatitis B, regardless of gender (29,30).

Our analysis has several weaknesses. Firstly, this analysis was a secondary study of data from the GBD 2019 study, and as with issues arising in other reports, the robustness and accuracy of the findings mainly rely on the quantity and quality of the input data. The GBD estimations were reconstructed through an algorithm based on many sources with different qualities, which (to some degree) could deviate with regard to the actual data (31). Secondly, the current study only examined the major risk factors for hepatitis B and C mortality, and detailed risk factors were

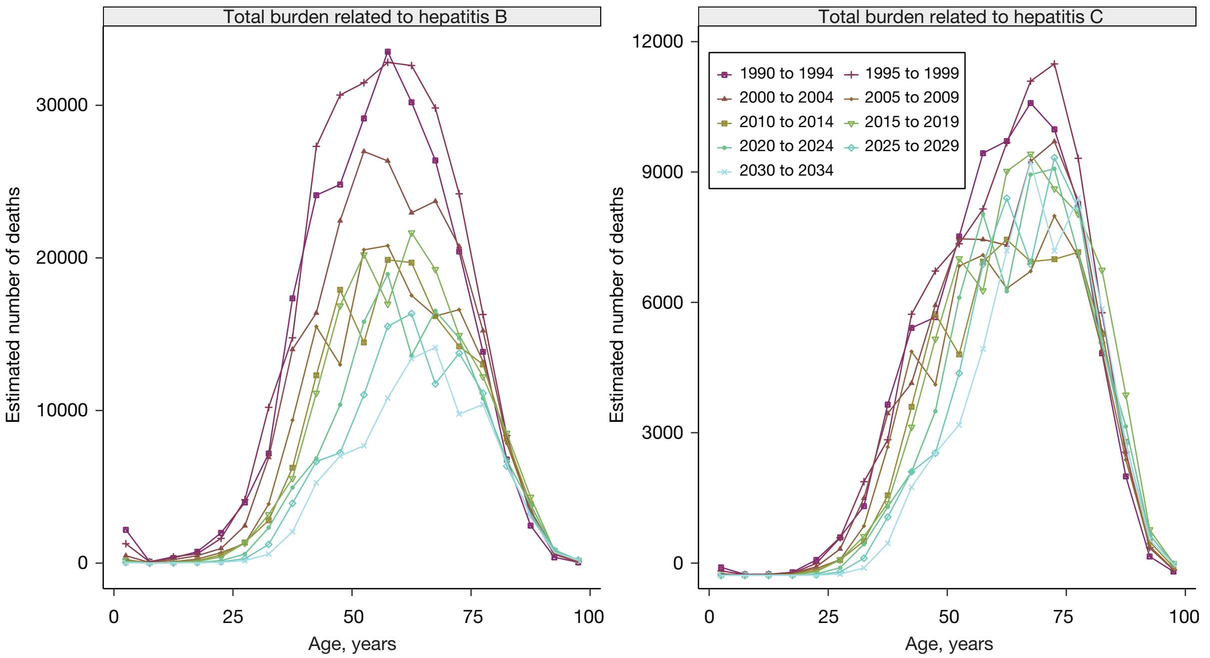

Figure 7 The projected mortality rates of hepatitis B and C in China from 1990 to 2034, divided into nine intervals.

not considered due to the lack of relevant data. These issues should be examined in a future study. Thirdly, impact of the ongoing pandemic would yield uncertainties surrounding the projecting outcomes, which has significantly changed the world including the mortality patterns and treatment patterns of hepatitis B and C. Fourthly, confounding between APC effects (the so-called identification problem) was intractable, which required the elimination of one of three temporal dimensions in APC analyses (11,32). Finally, some uncertainty surrounded the projected results due to the size and distribution of the population in China.

Conclusions

The mortality rate from hepatitis B and C substantially decreased from 1990 to 2019 in China. However, more national efforts, such as screening, vaccination, and antiviral treatment advances, should be strengthened in China to achieve the global hepatitis elimination targets.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-5676/rc

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5676/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Because this study does not contain personal or medical information about any identifiable living individuals, and animal subjects were not involved, the ethics approval and informed consent was waived by the Institutional Review Board of our hospital.

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