

Projected prevalence and mortality associated with alcohol-related liver disease in the USA, 2019–40: a modelling study

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Summary

Background Alcohol-related liver disease is the leading indication for liver transplantation in the USA. After remaining stable for over three decades, the number of deaths due to alcohol-related liver disease has been increasing as a result of increased high-risk drinking. We aimed to project trends in alcohol-related cirrhosis and deaths in the USA up to 2040 and assess the effect of potential changes in alcohol consumption on those trends.

Methods In this modelling study, we developed a multicohort state-transition (Markov) model of high-risk alcohol drinking patterns and alcohol-related liver disease in high-risk drinking populations born in 1900–2016 in the USA projected up to 2040. We used data from the National Epidemiologic Survey on Alcohol and Related Conditions, National Institute of Alcohol Abuse and Alcoholism, US National Death Index, National Vital Statistics System, and published studies. We modelled trends in alcohol-related liver disease under three projected scenarios: the status quo scenario, in which current trends continued; a moderate intervention scenario, in which trends in high-risk drinking reduced to 2001 levels under some hypothetical moderate intervention; and a strong intervention, in which trends in high-risk drinking decreased by 3–5% per year under some hypothetical strong intervention. The primary outcome was to project deaths associated with alcohol-related liver disease from 2019 to 2040 for each pattern of alcohol consumption under the different scenarios.

Findings Our model closely reproduced the observed trends in deaths due to alcohol-related liver disease from 2005 to 2018. Under the status quo scenario, age-standardised deaths due to alcohol-related liver disease are expected to increase from 8·23 (95% uncertainty interval [UI] 7·92–9·29) per 100 000 person-years in 2019 to 15·20 (13·93–16·19) per 100 000 person-years in 2040, and from 2019 to 2040, 1 003 400 (95% CI 896 800–1 036 200) people are projected to die from alcohol-related liver disease, resulting in 1 128 400 (1 113 200–1 308 400) DALYs by 2040. Under the moderate intervention scenario, age-standardised deaths due to alcohol-related liver disease would increase to 14·49 (95% UI 12·55–14·57) per 100 000 person-years by 2040, with 968 100 (95% UI 845 600–975 900) individuals projected to die between 2019 and 2040—35 300 fewer deaths than under the status quo scenario (a 3·5% decrease). Whereas, under the strong intervention scenario, age-standardised deaths due to alcohol-related liver disease would peak at 8·65 (95% UI 8·12–9·51) per 100 000 person-years in 2024 and decrease to 7·60 (6·96–8·10) per 100 000 person-years in 2040, with 704 300 (95% CI 632 700–731 500) individuals projected to die from alcohol-related liver disease in the USA between 2019 and 2040—299 100 fewer deaths than under the status quo scenario (a 29·8% decrease).

Interpretation Without substantial changes in drinking culture or interventions to address high-risk drinking, the disease burden and deaths due to alcohol-related liver disease will worsen in the USA. Additional interventions are urgently needed to reduce mortality and morbidity associated with alcohol-related liver disease.

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Introduction

Alcohol-related liver disease is now the leading indication for liver transplantation in the USA.¹ After remaining stable for over three decades, the number of alcohol-related cirrhosis deaths in the USA started increasing again in the 2000s.^{2,3} Recent increases in deaths due to alcohol-related liver disease are most pronounced in young age groups (25–34 years).³ Alcohol-related liver disease is also associated with a substantial economic burden.⁴ In 2015, a nationally

weighted measure of privately insured individuals found that approximately US\$5 billion of direct health-care costs were accrued by patients with cirrhosis related to alcohol-related liver disease, with a mean of \$44835 in per-person costs in the first year after diagnosis.⁴

Excessive consumption of alcohol remains the main cause of alcohol-related liver disease and associated complications and deaths.⁵ Since the 1950s, fewer than

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Research in context

Evidence before this study

We searched ProQuest, PubMed, AASLD, EASL, Biological Science Database, Wiley Online Library, and SpringerLink for abstracts and articles published in English between Jan 1, 2012, and Oct 10, 2019, using the search terms “high-risk drinking”, “alcohol use disorder”, “hepatitis”, “alcoholism”, “substance use”, “cirrhosis”, “hepatocellular carcinoma”, “liver cancer”, “liver disease related mortality”, “simulation”, and “projection”. Little data exist on the population-level burden of alcohol-related liver disease in the USA. To date, two studies had assessed mortality due to alcohol-related liver cirrhosis and liver cancer and one study has investigated increasing prevalences in the privately insured medical market in the USA. The Global Burden of Disease 2016 study attempted to project the burden of alcohol-related liver disease at a global level with a specific prediction for the USA until 2040. Although these studies have indicated that alcohol-related liver disease prevalence and mortality trends are changing,

none have attempted to project future mortality trends under different drinking rates. Although many groups have tried to simulate drinking behaviours, interventions, and the effect on alcohol-related harms in locations including Australia, Canada, Europe, and the UK, none has specifically assessed the USA.

Added value of this study

Our study is the first to provide data on the future consequences of the alcohol-related liver disease burden and deaths under different interventions on high-risk drinking in the USA.

Implications of all the available evidence

The findings of this study show that the current trends in high-risk drinking in the USA could further increase liver-related cirrhosis and mortality in the next two decades. Substantial changes in drinking culture and interventions to address high-risk drinking, like those implemented for smoking control since 1964, are necessary to curb alcohol-related liver disease trends.

20% of Americans have maintained abstinence from alcohol for their entire lives. Increases were seen in per-capita consumption, current drinking, and heavy episodic drinking worldwide from 1990 to 2017, with continued increases projected until 2030.⁶ From 2001 to 2012, data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) indicated that high-risk drinking and alcohol use disorder increased across the general population and in nearly all sociodemographic subgroups, with increases in high-risk drinking of 30% for the overall population, 16% for men, 58% for women, and more than 15% for all age groups.⁷ However, since the 1964 Surgeon General's Report *Smoking and Health* and the subsequent implementation of policies and social interventions, per-capita cigarette consumption has decreased by almost 75% over 40 years, implying that similar interventions in alcohol consumption might be possible with sufficient public and political will.⁸

Given the observed increases in alcohol consumption between 2000 and 2010 and deaths associated with alcohol-related liver disease among younger people (ie, aged 25–34 years),⁷ cirrhosis associated with alcohol-related liver disease and mortality are expected to further increase over time.³ Rates of progression of liver fibrosis can be even more pronounced in the presence of more than one risk factor—eg, hepatitis B and C.⁹ Although the evidence of alcohol's dose-response or threshold relationship with progression of liver fibrosis is unclear, even an average of two drinks or fewer per day can lead to progression of fibrosis.¹⁰ Despite increasing levels of alcohol consumption in all age groups and an increasing global burden of alcohol-related liver disease in terms of years of life lost,^{3,4,6,11} little data exist on the effect of reduction in high-risk drinking on the disease burden associated with

alcohol-related liver disease, particularly in the USA. Therefore, the objective of our study was to project trends in alcohol-related cirrhosis and deaths in the USA up to 2040 and assess the effect of potential changes in alcohol consumption on those trends.

Methods

Study design and model overview

In this modelling study, we developed a multicohort state-transition (Markov) alcohol simulation model that simulated the natural history of alcohol-related liver disease in the high-risk drinking population born between 1900 and 2016 until the year 2040 in the USA (figure 1). We used data from the NESARC for 2001–02 and 2012–13,⁷ National Institute on Alcoholism and Alcohol Abuse reports,¹² and published estimates on rates of progression of the natural history of alcohol-related liver disease.^{9,13} We calibrated unknown progression probabilities in the model to reproduce the observed trends in initiation of alcohol consumption,^{9,13} and deaths from cirrhosis associated with alcohol-related liver disease in the USA from 2012 to 2018. We then used the calibrated model to project temporal trends in alcohol-related cirrhosis, hepatocellular carcinoma, and deaths from 2019 to 2040. The model accounted for competing causes of mortality based on an individual's age and sex using US life tables,^{14,15} and cause-specific standardised adjustments to the risk of mortality for the top ten causes of age-specific and sex-specific mortality.¹⁶ Time advanced in our model in 1-year increments. We developed the model in R (version 3.22).

Data collection

The baseline population consisted of simulated high-risk drinking individuals born in the USA between

For US life tables see
www.mortality.org

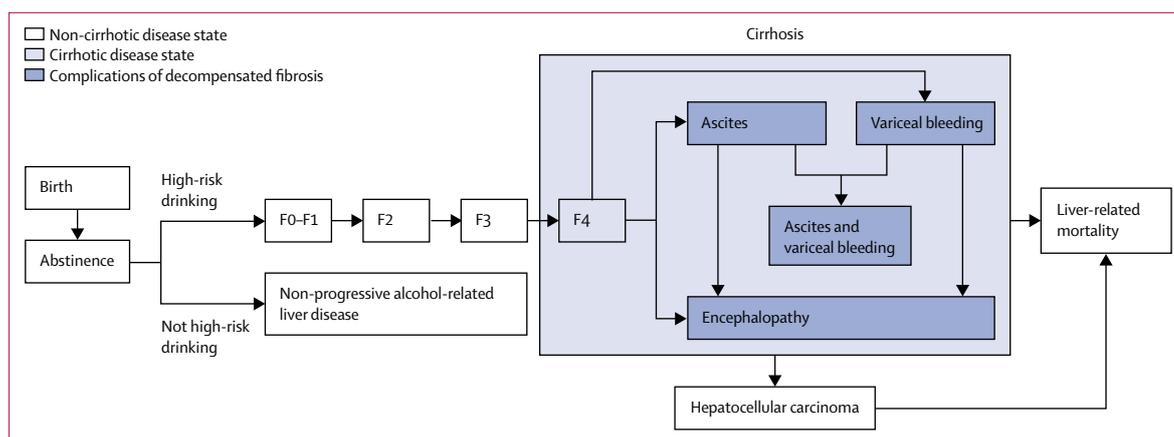


Figure 1: State-transition model of the natural history of alcohol-related liver disease

A patient is represented by one of the health states, shown here as squares. Arrows between states are annual transition probabilities. Competing-cause mortality and the probability of dying from other causes, both related and unrelated to alcohol use, exist in every state but are not shown in this figure for simplicity. F0=no fibrosis. F1=portal fibrosis without septa. F2=portal fibrosis with a few septa. F3=severe septal fibrosis. F4=compensated fibrosis.

1900 and 2016. We applied our estimated age of initiation of alcohol consumption in the US population and rates of high-risk drinking (defined as exceeding the recommended daily drinking limits at least weekly during the previous 12 months) by age-cohort and sex using historical data.⁷

For calibration of our model, we collected mortality data from the US Centers for Disease Control and Prevention (CDC) WONDER database for the years of interest (2012–18; only years with data available). We placed queries for International Classification of Diseases 10th revision (ICD-10) codes K70.0 (alcoholic fatty liver), K70.1 (alcoholic hepatitis), K70.2 (alcoholic fibrosis and sclerosis of liver), K70.3 (alcoholic cirrhosis of liver), K70.4 (alcoholic hepatic failure), and K70.9 (alcoholic liver disease) following procedures established for National Institute on Alcoholism And Alcohol Abuse surveillance reports on liver cirrhosis mortality in the USA.¹⁷

Natural history of alcohol-related liver disease

At any given time, patients occupied one health state and could transition to another state based on the progression rates. We used fibrosis stages to determine disease state, with F0 corresponding with the absence of scar tissue or fibrosis through to F1–F4 corresponding to the development of advanced scar tissue, fibrosis, cirrhosis, and complications of end-stage liver disease, such as hepatocellular carcinoma (figure 1). As people age, they remained in the abstinence state or transitioned to either non-high-risk drinking or high-risk drinking. High-risk drinkers could progress to the active phases of alcohol-related liver disease, which were defined by the following stages: no-to-mild fibrosis (F0–F1), moderate fibrosis (F2), and, finally, septal fibrosis (F3). Patients could further progress to compensated cirrhosis (F4), decompensated cirrhosis (ascites, variceal bleeding, ascites with variceal bleeding, and encephalopathy), and

hepatocellular carcinoma. From these advanced disease stages, patients could die due to liver-related mortality. We calibrated fibrosis progression from F0 to F4 using data from Poynard et al,⁹ which analysed 701 self-reported heavy drinkers in the preceding year who sought help at a French facility between January, 1982, and May, 1995. Of the 701 patients, 507 (72%) were men and the mean age at biopsy was 49 years (SD 13.5). We calibrated mortality from advanced states of liver disease from population studies that allowed for transplantation,¹⁸ therefore, although a transplantation state is not explicitly delineated in our model, we accounted for the competing event of transplantation before death.¹⁸

To account for changing exposure to alcohol, distribution of drinkers among the sexes and birth cohorts, we used published data based on the NESARC-III study.⁷ The NESARC-III study is a nationally representative survey of 36 309 US adults collected between April, 2012, and June, 2013. The survey data allow for estimates of the 2012–13 distribution of high-risk drinkers by age and sex. Compared with data collected 10 years earlier during NESARC-I, NESARC-III data also allowed for the consideration of changing rates of high-risk drinking among age groups.⁷ We estimated sex-dependent progression rates from pre-exposure state to development of advanced fibrosis (F1–F3),⁹ decompensated cirrhosis,¹⁸ and hepatocellular carcinoma¹⁹ from published studies.^{9,12} We estimated rates of disease progression in compensated cirrhosis, decompensated cirrhosis, and hepatocellular carcinoma from published observational studies.^{18,19}

Projection scenarios

To project model outcomes up to 2040, we considered three projection scenarios for high-risk drinking in the US population. Scenario one was a status quo scenario, which describes the absence of an intervention. This scenario assumed that age-specific rates of high-risk

For CDC WONDER website see <https://wonder.cdc.gov/>

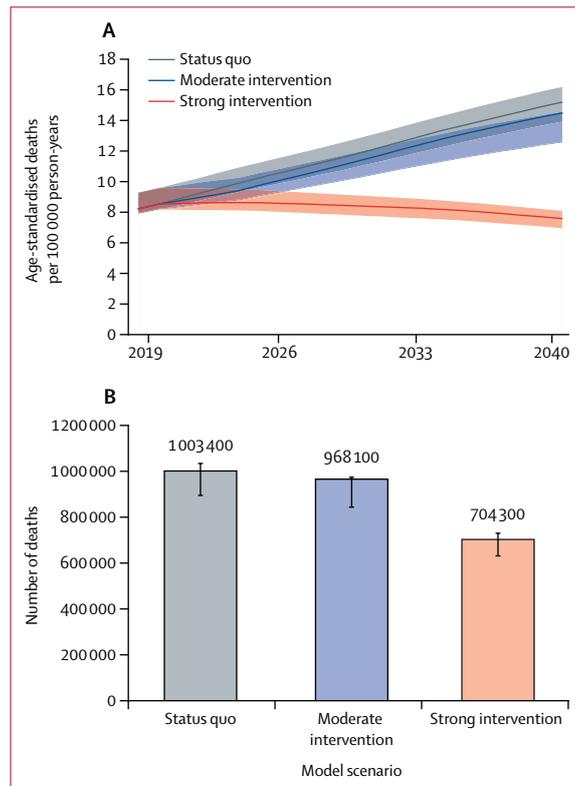


Figure 2: Model-predicted mortality due to alcohol-related liver disease in the USA, 2019–40

(A) Annual mortality, by scenario, with solid lines showing estimated mortality and shaded areas showing 95% uncertainty intervals. (B) Cumulative mortality by scenario, with error bars showing 95% uncertainty intervals.

drinking continue to increase following the trends reported by NESARC data from 2001–02 to 2012–13 (appendix p 1). Scenario 2 was a moderate intervention scenario, in which we modelled the implementation of a hypothetical intervention that would moderately reduce the rate of drinking. For this scenario we assumed that age-specific high-risk drinking rates return to 2001–02 levels as reported by NESARC, the lowest level of drinking observed in the past 20 years.⁷ The third scenario was a strong intervention scenario in which we modelled the implementation of a hypothetical strong intervention that would substantially reduce the rate of drinking. This scenario assumed a 3·5% decrease in rates of high-risk drinking every year starting from 2020 onwards. This scenario is based on the decrease in the rate of per-capita tobacco consumption after the publication of the 1964 Surgeon General's Report *Smoking and Health* and the subsequent implementation of policies and social interventions that led to a nearly three-quarter decrease in tobacco use over 40 years.²⁰ To implement the moderate intervention in the model, we decreased the 2019 rate of high-risk drinking to the levels in 2001 over 4 years (from 2020 to 2023), which was then followed by stable growth due to drinking initiation in younger cohorts. To implement the strong intervention

in the model, we decreased the 2019 rate of high-risk drinking by 3·5% per year from 2020 to 2040. The annual number of high-risk drinkers under each scenario is shown in the appendix (p 5).

Outcomes

The primary outcome was to project deaths associated with alcohol-related liver disease, exclusive of hepatocellular carcinoma mortality for calibration (2012–18) and inclusive of hepatocellular carcinoma mortality for projection, from 2019 to 2040 for each pattern of alcohol consumption under the different scenarios considered.

Secondary outcomes were to project the prevalence and incidence of decompensated cirrhosis and hepatocellular carcinoma, and disability-adjusted life-years (DALYs) lost to alcohol-related liver disease from 2019 to 2040. We calculated DALYs—a combined measure of mortality, prevalence of disease (in our case decompensated cirrhosis and hepatocellular carcinoma), and quantity of years of life lost (YLLs) due to disease and mortality²¹—using disability weights from Global Burden of Disease 2016 study values for decompensated cirrhosis and hepatocellular carcinoma (0 for scores of F0–F4, 0·178 for decompensated cirrhosis, and 0·540 for hepatocellular carcinoma).²² We estimated YLLs due to disease and mortality by multiplying each death by the remaining life expectancy at the age of death and summing across the year.

Sensitivity analysis

We did a probabilistic sensitivity analysis to determine the confidence in our model projections in each scenario given the joint uncertainty of model parameters, in particular transition rates, levels of high-risk drinking, and sex distributions (appendix pp 1–2). Using 1000 model outputs from the probabilistic sensitivity analysis, we generated the 95% uncertainty intervals (UIs) of model outcomes. We calculated age-standardised death rates using the 2000 US population as the standard age distribution. We present data in person-years, which correspond with standardisation to the US population, whereas data presented as men-years and women-years are standardised to the age–sex distribution of males and females in the 2000 US population.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data and had final responsibility to submit for publication.

Results

We validated our model-predicted annual mortality due to alcohol-related liver disease from 2012 to 2018 for men and women with those reported by the US national death registry data from the CDC WONDER database (appendix pp 3–4). Our projected liver disease mortality

See Online for appendix

(exclusive of hepatocellular carcinoma) due to alcohol-related liver disease was within 1·8% (95% UI 1·2–2·4) of the CDC reported deaths from 2012 to 2018 for both sexes combined.

Under the current high-risk drinking rates (status quo scenario), annualised age-standardised deaths due to alcohol-related liver disease are projected to increase from 8·23 (95% UI 7·92–9·29) per 100 000 person-years in 2019 to 15·20 (13·93–16·19) per 100 000 person-years in 2040, an 84% increase from 2019 (figure 2). In men, the number of age-standardised deaths per 100 000 men-years is projected to increase from 10·11 (95% UI 10·04–10·18) in 2019 to 17·71 (17·60–17·82) in 2040—a 75% increase—and in women, the corresponding number of deaths per 100 000 women-years is projected to increase from 6·34 (6·29–6·38) in 2019 to 12·59 (12·51–12·67) in 2040—a 99% increase. From 2019 to 2040, under the status quo scenario, 1 003 400 (95% CI 896 800–1 036 200) individuals are projected to die from alcohol-related liver disease in the USA, with 35% of deaths occurring in individuals younger than 55 years (figures 2 and 3).

Under the moderate intervention scenario, age-standardised deaths due to alcohol-related liver disease would increase to 14·49 (95% UI 12·55–14·57) per 100 000 person-years in 2040, a 76% increase from 2019, and 968 100 (95% UI 845 600–975 900) individuals are projected to die from alcohol-related liver disease between 2019 and 2040 in the USA (figure 2). This intervention scenario resulted in 35 300 fewer deaths than the status quo scenario—ie, a 3·5% decrease.

Under the strong intervention scenario, age-standardised deaths due to alcohol-related liver disease are projected to peak at 8·65 (95% UI 8·12–9·51) per 100 000 person-years in 2024 and decrease to 7·60 (6·96–8·10) per 100 000 person-years in 2040, a 7·6% decrease from 2019, and 704 300 (95% CI 632 700–731 500) individuals are projected to die from alcohol-related liver disease between 2019 and 2040 in the USA. This intervention scenario results in 299 100 fewer deaths than the status quo scenario—ie, a 29·8% decrease. Notably, deaths due to alcohol-related liver disease in men are projected to decrease by 12·5%, from 10·11 (95% UI 10·04–10·18), per 100 000 men-years in 2019 to 8·85 (8·80–8·91) per 100 000 men-years in 2040, and the corresponding deaths in women would decrease by 0·6%, from 6·34 (6·29–6·38) per 100 000 women-years in 2019 to 6·30 (6·26–6·33) per 100 000 women-years in 2040.

We also projected that deaths due to alcohol-related liver disease would be reduced in all age groups due to the reduction in high-risk drinking, with 28% fewer deaths in the strong intervention scenario than in the status quo scenario occurring between those aged 25 years and 54 years (figure 3), the age group with the most pronounced effect on overall DALYs.

Alcohol-related liver disease is also associated with substantial DALYs. In 2019, alcohol-related liver disease

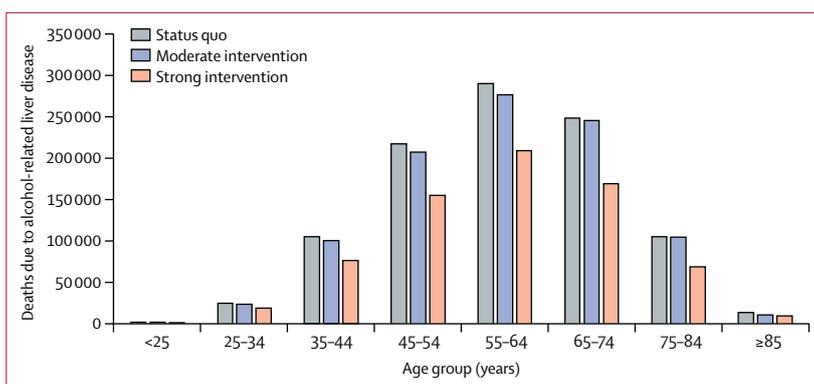


Figure 3: Deaths due to alcohol-related liver disease by intervention scenario among high-risk drinkers in the USA by age group, 2019–40

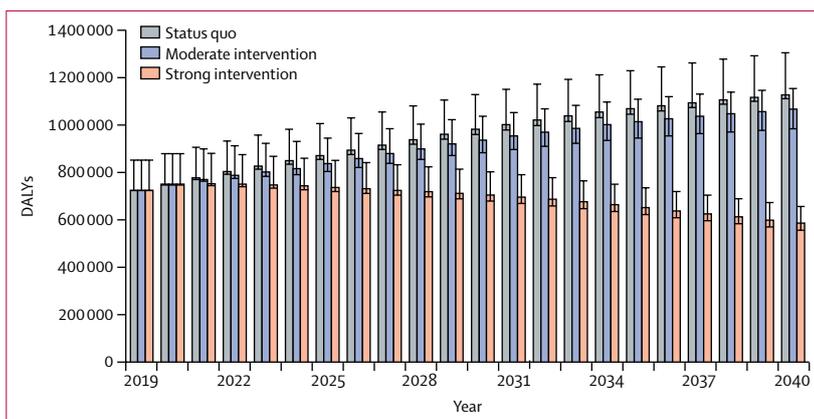


Figure 4: Model-predicted annual DALYs for alcohol-related liver disease by intervention scenario among high-risk drinkers in the USA, 2019–40

Error bars show 95% uncertainty intervals. DALYs=disability-adjusted life-years.

resulted in 726 500 DALYs (95% CI 721 900–854 300), which is projected to increase to 1 128 400 (1 113 200–1 308 400) by 2040 under the status quo scenario, a 55% increase compared with 2019 (figure 4). Between 2019 and 2040, cumulatively, 21·0 million (20·7–24·3) DALYs would be attributable to alcohol-related liver disease in the USA. The moderate intervention scenario is projected to result in 20·2 million (19·1–22·5) DALYs between 2019 and 2040, 0·8 million fewer than the status quo scenario—ie, a 3·8% decrease. And the strong intervention scenario is projected to result in 15·3 million (14·8–17·4) DALYs for the same period, 4·7 million fewer DALYs than the status quo scenario—ie, a 27% decrease.

Under the status quo scenario, the age-standardised incidence of decompensated cirrhosis associated with alcohol-related liver disease is projected to increase from 9·9 cases (95% CI 9·3–10·9) per 100 000 person-years in 2019 to 17·5 cases (15·8–18·4) per 100 000 person-years in 2040, a 77% increase compared with 2019. The age-standardised incidence of hepatocellular carcinoma associated with alcohol-related liver disease is projected to increase from 1·1 cases (1·1–1·3) per 100 000 person-years

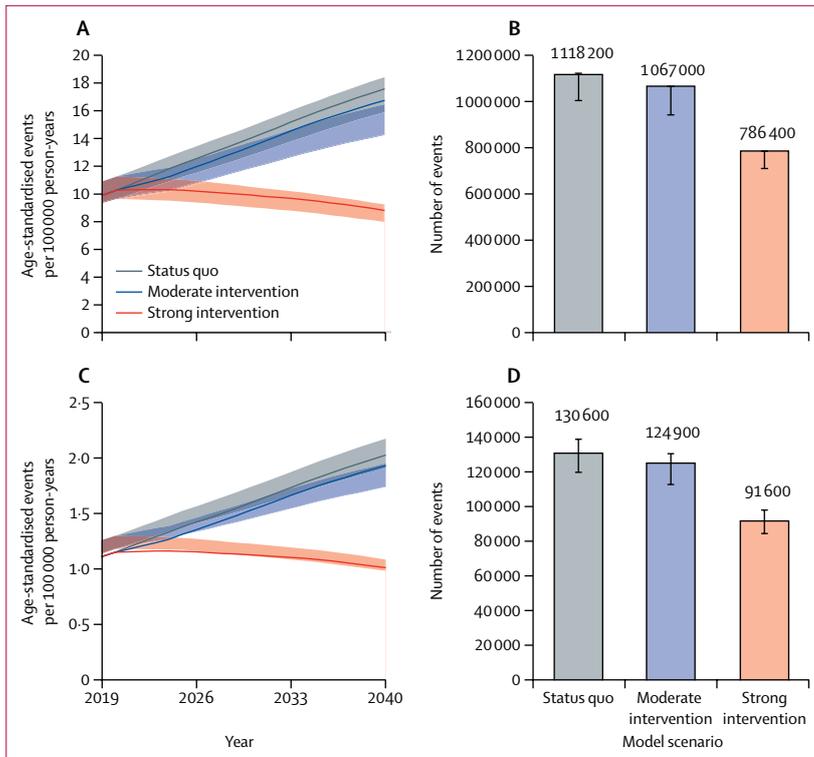


Figure 5: Projected cases of decompensated cirrhosis (A, B) and hepatocellular carcinoma (C, D) associated with alcohol-related liver disease under different scenarios in high-risk drinkers in the USA, 2019–40

The annualised age-standardised incidence of decompensated cirrhosis (A) and hepatocellular carcinoma (C), by year, are shown with the solid line indicating the incidence estimate and shaded area showing the 95% CI. The cumulative number of cases of decompensated cirrhosis (B) and hepatocellular carcinoma (D) are shown as bar charts, with error bars showing 95% CIs.

in 2019 to 2.0 cases (1.9–2.2) per 10000 person-years in 2040, a 90% increase (figure 5). The 55–64 years age group is projected to have the highest proportion of new cases of decompensated cirrhosis and hepatocellular carcinoma associated with alcohol-related liver disease from 2019 to 2040 (data not shown). Under the moderate intervention scenario, the age-standardised incidence of decompensated cirrhosis is projected to increase to 16.7 cases (95% CI 14.2–16.4) per 100000 person-years in 2040, a 69% increase compared with 2019, and of hepatocellular carcinoma is projected to increase to 1.9 cases (1.7–2.0) per 100000 person-years, a 73% increase compared with 2019. Under the strong intervention scenario, the corresponding incidence of decompensated cases is projected to decrease to 8.8 cases (7.9–9.2) per 10000 person-years in 2040, an 11% decrease compared with 2019, and of hepatocellular carcinoma is projected to decrease to 1.0 cases (1.0–1.1) per 10000 person-years, a 90% decrease compared with 2019.

Between 2019 and 2040, the cumulative incidence of decompensated cirrhosis associated with alcohol-related liver disease was projected to decrease from 1 118 200 cases (95% CI 1 005 400–1 123 500) under the status quo scenario to 1 067 000 (943 400–1 084 600)

under the moderate intervention scenario (a 4.6% decrease), and to 786 400 case (711 200–819 300) under the strong intervention scenario (a 30% decrease). Similarly, the cumulative incidence of hepatocellular carcinoma associated with alcohol-related liver disease was projected to decrease from 130 600 cases (119 600–138 600) under the status quo scenario to 124 900 (112 600–130 300) under the moderate intervention scenario (a 4.4% decrease), and 91 600 cases (84 400–97 900) under the strong intervention scenario (a 30% decrease).

Discussion

Increasing rates of heavy alcohol consumption are a threat to public health in the USA. Without any changes in trends in alcohol consumption, we projected that the annual age-standardised mortality due to alcohol-related liver disease would increase by 75% by 2040. We also projected that from 2019 to 2040 just over 1 million individuals could die from alcohol-related liver disease, of whom 35% are projected to be younger than 55 years. Additionally, the age-standardised incidence of alcohol-related decompensated cirrhosis and hepatocellular carcinoma are projected to increase by more than 65% by 2040. Policies to curb these trends are needed. Most importantly, we found that an intervention that can accomplish a 3.5% reduction in the rate of high-risk drinking annually, could avert the adverse trends and reduce deaths due to alcohol-related liver disease by up to 30% by 2040.

Given the paucity of surveillance data on liver damage associated with alcohol-related liver disease in the US population, our study provides an approximation of active disease progression and prevalence in the USA. As a disease that develops slowly, understanding how demographic changes might affect long-term trends is important. Two main reasons exist for the increased mortality observed from diseases associated with alcohol-related liver disease. First, the demographics of high-risk drinkers has changed. In comparison with previous generations, the number of high-risk drinkers within each age group has increased, and the prevalence of high-risk drinking among women has also increased.⁷ Second, overall life expectancy is higher than for previous generations (ie, decreasing competing mortality), providing an opportunity for the development of advanced stages of alcohol-related liver disease, such as hepatocellular carcinoma, among high-risk drinkers.

Our study highlights the need to bring alcohol-related liver disease to the forefront of policy discussions. By contrast with deaths due to opioid overdose, little attention has been given to the role of alcohol-related liver disease in the so-called deaths of despair in the USA.²³ With substantial investment of government resources to address the opioid epidemic, deaths due to opioid overdoses could decrease substantially in the near future. We believe similar investment of funding for alcohol-related liver disease is needed to curb increasing trends in associated deaths.

The USA has previously dealt with impending health crises due to substance abuse. Rigorous scientific study on the effects of smoking and policy experimentation has led to substantial improvements in US health-care results related to smoking cessation. Our study highlights the potential for a similar approach to alleviate some of the projected future disease burden due to alcohol-related liver disease. Although mortality patterns for alcohol-related liver disease in the USA are changing,³ to our knowledge, no projection of future mortality trends has been done. Further research needs to focus on the likelihood of developing cirrhosis as a high-risk drinker. With life expectancy now reaching 80–90 years, current recommendations on drinking might substantially underestimate the risk profile for current middle-aged adults to develop alcohol-related liver disease in later life.

The effectiveness of interventions directed at individuals with alcohol-related liver disease is reduced by its late presentation, when clinical options are restricted. Many, if not most, people with alcohol-related liver disease are diagnosed at a late stage, frequently with advanced or decompensated cirrhosis,^{18,24} when the only effective strategies to improve survival are sobriety and liver transplantation, with many patients who achieve sobriety still needing transplantation. Our model projects an increase in the incidence of decompensated cirrhosis associated with alcohol-related liver disease of 77% over the next 20 years. Early interventions are needed to forestall the development of cirrhosis in the first place; however, most patients present with alcohol-related liver disease at age 40–50 years.² Therefore, to reverse these trends clinical interventions and novel pharmacological treatments are urgently needed for alcohol use disorder in patients who have advanced liver disease.

Population-level interventions targeted at drinking generally might be effective in reducing high-risk drinking. For instance, the Alcohol Policy Scale, a tool developed to grade the efficacy and implementation of alcohol policies in a given US State, has been used to explain variation in between-State binge drinking prevalence.²⁵ Although further work is needed to understand the relative importance of particular policies on high-risk drinking specifically, policies that focus on the general population, alcohol consumption, and increasing the price of alcohol or reducing availability of alcohol might have independent associations with reducing binge drinking.^{26,27}

Additional research is needed into the transferability of other interventions to decrease tobacco use and their effectiveness in the alcohol setting, including changes in mass-media regulations, advertising restrictions, and developmentally appropriate school-based programmes.^{26,28,29} Community-based participatory research as a health promotion approach has been shown to be effective in reducing population trends in alcohol use in a relatively small and homogenous population.³⁰

The extension of policies promoting community-based research in the whole European Union through the Youth in Europe campaign,³⁰ should be studied as a potential programme to be used in the US environment. One potential extension of this work is to study the cost-effectiveness trade-offs in the short, medium, and long term between these targeted and general approaches to decreasing levels of drinking in the US population.

Our study had several limitations, and so the data we present here must be interpreted in the context of the study design. First, our model was calibrated against the fibrosis disease progression of lifetime drinkers with 1 year of documented heavy drinking before a liver biopsy. These drinkers were from a French study, which might not correspond with the risks incurred with US high-risk drinkers from the general population. Second, our study used aggregated data from the NESARC study.⁷ The aggregated data restrict our ability to specify the age at first drink in our model according to the specific drinking pattern of high-risk drinkers. The overall mortality trends in our model are robust to different distributions of age at first drink but age-specific distributions of mortality are sensitive to these parameters, so increasing our uncertainty intervals. Third, we made assumptions regarding rates of high-risk drinking in the birth cohorts from 1995–2016. The bulk of mortality due to cirrhosis associated with alcohol-related liver disease historically occurs in cohorts older than 35 years, thus any inaccuracy in our estimates of high-risk drinking in people younger than 35 years should have had little effect on our overall results. Fourth, our results are dependent on survey data of socially stigmatised behaviours, specifically high-risk drinking, which, although accounted for in our sensitivity analysis, could lead to a conservative estimate of projected mortality. Fifth, our model did not account for comorbid diseases such as hepatitis B and C, which can increase the incidence of fibrosis. Sixth, while Markov models have many strengths, such as simplicity in defining health states, one of their limitations is that they follow so-called memoryless property—ie, the rate of disease progression is dependent on the current state only, and not on prior history. Finally, we did not account for the under-reporting of deaths due to alcohol-related liver disease, leading to a potential underestimation of mortality projections in our model.³¹ Cumulatively, these limitations indicate that our study provides a conservative estimate of the true disease burden and mortality associated with alcohol-related liver disease in the USA.

In summary, by use of a clinically valid mathematical model that accounted for changes in demographics of the high-risk drinking population, our study predicts that cirrhosis, hepatocellular carcinoma, and deaths associated with alcohol-related liver disease are expected to increase substantially in the USA in the next two decades. Specifically, alcohol-related liver disease is likely to continue to increase among younger birth cohorts

and women. Substantial changes in drinking culture or interventions to address high-risk drinking are needed to curb the trajectory of the disease burden associated with alcohol-related liver disease.

Contributors

JJ, TA, and JC contributed to the study concept and design. JJ, TA, and JC drafted the manuscript. All authors contributed to critical revision of the manuscript for important intellectual content. JJ did the statistical analyses. All authors contributed to interpretation of the data.

Declaration of interests

TA reports personal fees from Value Analytics Labs outside of the submitted work. EBT reports personal fees from Kaleido, Rebiotix, Bausch, Allergan, and Axcella outside of the submitted work. JC reports personal fees from Value Analytics Labs and WHO, grants and personal fees from Gilead Sciences, and grants from Merck outside of the submitted work. All other authors declare no competing interests.

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References

- Cholankeril G, Ahmed A. Alcoholic liver disease replaces hepatitis C virus infection as the leading indication for liver transplantation in the United States. *Clin Gastroenterol Hepatol* 2018; **16**: 1356–58.
- Basra S, Anand BS. Definition, epidemiology and magnitude of alcoholic hepatitis. *World J Hepatol* 2011; **3**: 108–13.
- Tapper EB, Parikh ND. Mortality due to cirrhosis and liver cancer in the United States, 1999–2016: observational study. *BMJ* 2018; **362**: k2817.
- Mellinger JL, Shedden K, Winder GS, et al. The high burden of alcoholic cirrhosis in privately insured persons in the United States. *Hepatology* 2018; **68**: 872–82.
- Rehm J, Taylor B, Mohapatra S, et al. Alcohol as a risk factor for liver cirrhosis: a systematic review and meta-analysis. *Drug Alcohol Rev* 2010; **29**: 437–45.
- Manthey J, Shield KD, Rylett M, Hasan OSM, Probst C, Rehm J. Global alcohol exposure between 1990 and 2017 and forecasts until 2030: a modelling study. *Lancet* 2019; **393**: 2493–502.
- Grant BF, Chou SP, Saha TD, et al. Prevalence of 12-month alcohol use, high-risk drinking, and DSM-IV alcohol use disorder in the United States, 2001–2002 to 2012–2013: results From the National Epidemiologic Survey on Alcohol and Related Conditions. *JAMA Psychiatry* 2017; **74**: 911–23.
- Flaherty L. Achievements in public health, 1900–1999: tobacco use-United States, 1900–1999. *J Emerg Nurs* 2000; **26**: 150–51.
- Poynard T, Mathurin P, Lai C-L, et al. A comparison of fibrosis progression in chronic liver diseases. *J Hepatol* 2003; **38**: 257–65.
- Singal AK, Anand BS. Recent trends in the epidemiology of alcoholic liver disease. *Clin Liver Dis (Hoboken)* 2013; **2**: 53–56.
- GBD 2016 Alcohol Collaborators. Alcohol use and burden for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2018; **392**: 1015–35.
- US Department of Health and Human Services. 10th Special Report to the US Congress on alcohol and health. Bethesda, MD: National Institute on Alcohol Abuse and Alcoholism, 2000.
- Mathurin P, Beuzin F, Louvet A, et al. Fibrosis progression occurs in a subgroup of heavy drinkers with typical histological features. *Aliment Pharmacol Ther* 2007; **25**: 1047–54.
- US Census Bureau. Population estimates and projection, annual estimates of the resident population by single year of age and sex for the United States: April 1, 2010 to July 1, 2017. <https://www.census.gov/data/datasets/2017/demo/popest/nation-detail.html> (accessed May 1, 2018).
- US Census Bureau. Population Estimates and Projection, Intercensal estimates of the resident population by single year of age, sex, race, and Hispanic origin for the United States: April 1, 2000 to July 1, 2010. <https://www.census.gov/data/datasets/timeseries/demo/popest/intercensal-2000-2010-national.html> (accessed May 1, 2018).
- Roerecke M, Rehm J. Cause-specific mortality risk in alcohol use disorder treatment patients: a systematic review and meta-analysis. *Int J Epidemiol* 2014; **43**: 906–19.
- Yoon Y-H, Chen CM. Surveillance report# 105: liver cirrhosis mortality in the United States: national, state, and regional trends, 2000–2013. Bethesda, MD: National Institute on Alcohol Abuse and Alcoholism, 2016.
- Jepsen P, Ott P, Andersen PK, Sørensen HT, Vilstrup H. Clinical course of alcoholic liver cirrhosis: a Danish population-based cohort study. *Hepatology* 2010; **51**: 1675–82.
- Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology* 2004; **127** (suppl 1): S35–50.
- US Health Department of Health. Let's make the next generation tobacco-free: your guide to the 50th anniversary surgeon general's report on smoking and health. Atlanta, GA: Centers for Disease Control and Prevention, 2014.
- Murray CJ. Quantifying the burden of disease: the technical basis for disability-adjusted life years. *Bull World Health Organ* 1994; **72**: 429–45.
- GBD 2016 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017; **390**: 1260–344.
- Case A, Deaton A. Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century. *Proc Natl Acad Sci USA* 2015; **112**: 15078–83.
- Schütte K, Bornschein J, Kahl S, et al. Delayed diagnosis of HCC with chronic alcoholic liver disease. *Liver Cancer* 2012; **1**: 257–66.
- Naimi TS, Blanchette J, Nelson TF, et al. A new scale of the U.S. alcohol policy environment and its relationship to binge drinking. *Am J Prev Med* 2014; **46**: 10–16.
- Xuan Z, Blanchette JG, Nelson TF, et al. Youth drinking in the United States: relationships with alcohol policies and adult drinking. *Pediatrics* 2015; **136**: 18–27.
- Xuan Z, Blanchette J, Nelson TF, Heeren T, Oussayef N, Naimi TS. The alcohol policy environment and policy subgroups as predictors of binge drinking measures among US adults. *Am J Public Health* 2015; **105**: 816–22.
- Stockings E, Hall WD, Lynskey M, et al. Prevention, early intervention, harm reduction, and treatment of substance use in young people. *Lancet Psychiatry* 2016; **3**: 280–96.
- Onrust SA, Otten R, Lammers J, Smit F. School-based programmes to reduce and prevent substance use in different age groups: what works for whom? Systematic review and meta-regression analysis. *Clin Psychol Rev* 2016; **44**: 45–59.
- Kristjansson AL, Sigfusdottir ID, Thorlindsson T, Mann MJ, Sigfusson J, Allegrante JP. Population trends in smoking, alcohol use and primary prevention variables among adolescents in Iceland, 1997–2014. *Addiction* 2016; **111**: 645–52.
- Asrani SK, Larson JJ, Yawn B, Therneau TM, Kim WR. Underestimation of liver-related mortality in the United States. *Gastroenterology* 2013; **145**: 375–82.