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Letter to the Editor

Sex-specific trends and demographic vs. epidemiologic drivers of alcohol-related cirrhosis in United States, 2021–2040: Letter to the editor on "Sex disparities in alcohol-associated liver disease and subtype differences in alcohol-attributable cancers in the United States"

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Keywords: Alcohol-related cirrhosis; Sex-specific trajectories; Demographic-versus-epidemiologic drivers; United States

Dear Editor,

The elegant analysis by Danpanichkul et al. in *Clinical and Molecular Hepatology* showed that from 2000 to 2021 the age-standardised death rate (ASDR) of alcohol-associated liver disease (ALD) in the United States rose by 79%, with a steeper slope in women than in men.[1] Whether this sex gap will persist—and to what extent future trends are shaped by demography versus changing age-specific risk—has not been explored. We therefore used Global Burden of Disease (GBD 2021) data to project incidence and prevalence of alcohol-related cirrhosis to 2040 and to disentangle the relative contributions of population ageing, population growth, and epidemiologic change.

GBD 2021 estimates for cirrhosis due to alcohol were downloaded from the Global Health Data Exchange.[2] We fitted Bayesian age–period–cohort (BAPC) models separately for males, females, and both sexes combined, using 1990–2021 data as training input and assuming random-walk priors on period and cohort effects. Posterior predictive distributions yielded age-standardised incidence and prevalence for each year through 2040. We then applied Das Gupta's[3] three-component decomposition to quantify the relative contributions of (i) population ageing, (ii) population size, and (iii) epidemiologic change (i.e., variation in age-specific rates independent of demography) to the absolute difference between 1990 and 2021. Uncertainty intervals (UIs) represent the 2.5th–97.5th percentiles of 2,000 posterior draws.

The male incidence curve plateaued: 8.65 per 100,000 in 2040 (95% UI –4.7–22.1) versus 8.53 in 2021 (+1.4 %; average annual percent change [AAPC] +0.1%). Female incidence nearly doubled, rising from 2.96 to 5.71 per 100,000 (+93%; AAPC +3.5%). Combined, incidence climbed 62% to 9.11 per 100,000 (Supplementary Table 1, Supplementary Fig. 1A; Supplementary Fig. 1A–1B show overall [sex-

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combined] rates; sex-specific estimates are presented in Fig. 1 and Supplementary Tables 1–3).

Prevalence accelerated for both sexes but far faster for women (AAPC +6.3%) than for men (+3.3%). By 2040 the projected point estimates reach 113.3 per 100,000 (men) and 94.1 per 100,000 (women), reflecting relative increases of 84% and 219%, respectively(Supplementary Table 2, Supplementary Fig. 1B).

Figure 1 summarises component contributions (Decomposition of changes in alcohol related cirrhosis deaths due to population growth, population ageing and epidemiologic change rate in United States, 1990–2021). See Supplementary Table 3 for detailed data.

Deaths: additional 10,650 deaths (both sexes) are anticipated; 85% stem from demography and 15% from adverse epidemiologic drift. Among women, epidemiologic deterioration explains 35% of excess deaths.

Disability-adjusted life-years (DALYs): net increase of 281,917 DALYs, 90% attributable to demography; epidemiologic change offsets 7% in men but adds 36% in women.

Incidence: ageing and growth account for virtually all of the male increment but only 87% in females, where epidemiology contributes a further 13%.

Prevalence: in men, demographic factors are opposed by a large negative epidemiologic term (–78%), whereas in women the epidemiologic term is positive (+9%).

Our projections extend the worrisome female-predominant rise in ALD documented by Danpanichkul et al. into

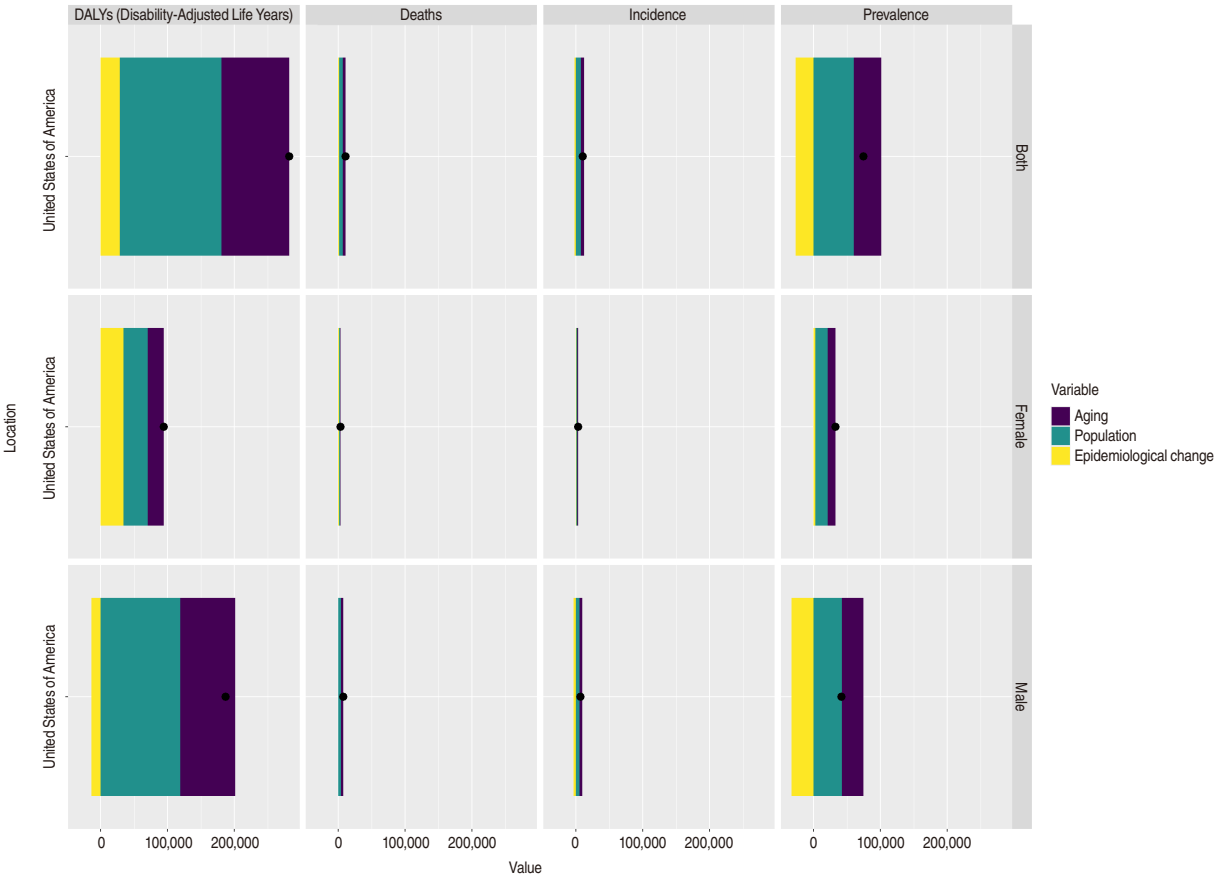

Figure 1. Decomposition of changes in alcohol related cirrhosis deaths due to population growth, population ageing and epidemiologic change rate in United States, 1990–2021.

Abbreviations:

AAPC, average annual percent change; ALD, alcohol-associated liver disease; ASDR, age-standardised death rate; BAPC, Bayesian age–period–cohort; DALYs, disability-adjusted life-years; GBD, Global Burden of Disease; UIs, uncertainty intervals

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the next two decades. Incidence in men appears to have reached a plateau, but the steep, demography-independent ascent in women signals an emerging convergence of sex-specific burdens. Sociobehavioural data—showing faster increases in high-risk drinking among US women—align with the positive epidemiologic component we observed for female deaths, DALYs and incidence.[4-6]

That demography alone would enlarge the absolute ALD burden even under stable age-specific rates underscores the indispensability of primordial prevention: curbing harmful alcohol use before liver injury becomes entrenched. Yet the sizeable, sex-specific epidemiologic contributions highlight additional levers—earlier detection of advanced fibrosis, universal hepatitis vaccination, and equitable access to pharmacologic treatment of alcohol-use disorder—that can bend the female trajectory.

Our study inherits the limitations of the GBD modelling cascade (e.g., misclassification of underlying cause) and the wide UIs arising from long-range forecasting. Nevertheless, sensitivity analyses using alternative priors yielded qualitatively similar sex patterns.

Without intensified, gender-responsive interventions, the United States will face a tripling of alcohol-related cirrhosis prevalence by 2040, driven predominantly by women, while deaths and DALYs will continue to grow primarily because the population is older and larger. Policies that reduce alcohol exposure across the life-course, coupled with scaled-up screening and treatment programmes targeted to women, are urgently needed to avert the impending surge.

Author's contributions

Kui Wang (KW): Formulated the research question, retrieved and cleaned the GBD 2021 cirrhosis data, implemented all statistical analyses and the Das Gupta decomposition in R (version 4.4.0), produced the figures and supplementary tables, and drafted the initial manuscript. Yunqing Zeng (YZ, corresponding author): Provided overall study conception and methodological oversight, independently verified the R code and results, contextualised the findings from clinical and public-health perspectives, critically revised the manuscript for substantive intellectual content, and secured the resources required to complete the project. Both authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

Data availability

All data analysed in the present study are publicly available from the Global Burden of Disease 2021 repository (Institute for Health Metrics and Evaluation). The full dataset can be accessed and downloaded at https://ghdx.healthdata.org/gbd-2021.

Conflicts of Interest

The authors have no conflicts to disclose.

SUPPLEMENTARY MATERIAL

Supplementary material is available at Clinical and Molecular Hepatology website (http://www.e-cmh.org).

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