

Heavy daily alcohol intake at the population level predicts the weight of alcohol in cirrhosis burden worldwide

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Background & Aims: Studies assessing alcohol as a population level risk factor for cirrhosis typically focus on per capita consumption. However, clinical studies indicate that daily intake is a strong predictor of alcoholic cirrhosis. We aimed to identify the determinants of alcohol's contribution to the global cirrhosis burden and to evaluate the influence of daily drinking on a population level.

Methods: We performed a comprehensive analysis of the WHO 2014 Global Status Report on Alcohol and Health. We categorized countries by heavy or moderate drinking based on daily consumption, using U.S. Department of Agriculture definitions of heavy drinking. Additional data on cirrhosis cofactors were also obtained. Uni- and multivariate models were fitted to identify independent predictors of the alcohol-attributable fraction of cirrhosis.

Results: The WHO 2014 Report found that half of cirrhosis mortality worldwide is attributable to alcohol, approximating 60% in North America and Europe. In an integrative multivariate model, the designation of countries by moderate or heavy daily drinking had the strongest influence on the weight of alcohol in the cirrhosis burden. The relative contribution from alcohol increased by 11% with a transition from the moderate to heavy classification ($p < 0.001$). Importantly, drinking patterns such as heavy episodic drinking and the type of alcohol did not independently predict the alcohol-attributable fraction of cirrhosis.

Conclusions: Heavy daily drinking on a population level significantly influences the weight of alcohol in the cirrhosis burden. Reducing heavy drinking should be considered as an important target for public health monitoring and policies.

Lay summary: We carried out an analysis of the WHO 2014 Global Status Report on Alcohol and Health, and categorized countries by their level of drinking (heavy or moderate). We found that half of the global cirrhosis cases, and 60% in both North America and Europe are associated with alcohol intake. We concluded that on a population level heavy daily drinking significantly influences the impact of alcohol on the cirrhosis burden. © 2016 European Association for the Study of the Liver. Published by Elsevier B.V. All rights reserved.

Introduction

Excessive use of alcohol is a main cause of global mortality, contributing to deaths through cancers, toxic organ damage, and accidents and injuries [1]. Detailed data on the burden of alcohol-associated mortality were released in the 2014 World Health Organization (WHO) Global Status Report on Alcohol and Health, which is the most detailed and comprehensive report of this kind [2]. This publication emphasizes the significant contribution alcohol use makes to the global cirrhosis burden, with approximately half of global cirrhosis deaths attributed to alcohol use. Attention should be placed on detrimental patterns and levels of alcohol use that lead to cirrhosis in order to reduce associated mortality.

Previous studies have demonstrated a dose-response relationship between alcohol intake and an individual's risk for developing cirrhosis [3–6]. There is also substantial support for a threshold effect, wherein the risk for developing cirrhosis is constant over time if a threshold of intake is surpassed [7–9]. For a given level of total consumption, the pattern of drinking may confer higher risk for cirrhosis; for example, drinking on a daily basis has been shown to be associated with higher risk [6,7,9]. Some studies have investigated the potential influences of factors including binge drinking [10,11], duration of consumption over lifetime [7,9], and alcohol type [6,12,13]. Cofactors that have been shown to increase risk of alcoholic cirrhosis include cigarette smoking [14,15], excess weight [16], and viral hepatitis [17]. Consumption of certain substances, such as coffee and tea, may provide a protective effect against the development of liver

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Abbreviations: WHO, World Health Organization; AAF, alcohol-attributable fraction; ASDR, age-standardized death rate; HCV, hepatitis C virus; HBV, hepatitis B virus; GDP, gross domestic product; BMI, body mass index.



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disease [18,19]. For all variables discussed, the potential for significant geographical variation exists, due to cultural and socioeconomic differences in exposure to risk or protective factors. The economics and policies of alcohol sale can also be expected to vary considerably across the globe and to influence the way it is consumed [20].

On a population level, an association between alcohol consumption and cirrhosis mortality has been well documented, reflecting the risk relationship demonstrated on the individual level [21–24]. Most population level studies have assessed the effect of per capita drinking on the death rate from cirrhosis, primarily in Europe and the U.S. One study compared the effect of per capita consumption on cirrhosis mortality in European countries that predominantly consume spirits as opposed to wine and beer [21]. Moreover, it has been hypothesized that differences in population drinking patterns (e.g., heavy episodic vs. daily drinking) shape the relationship between alcohol consumption and cirrhosis mortality [22]. However, to our knowledge, there are no studies assessing the influence of daily drinking patterns on cirrhosis mortality at the population level, or on the burden of alcoholic cirrhosis specifically. In this study, we aimed to identify the main determinants of cirrhosis mortality and the weight of alcohol in the global cirrhosis burden. We used recent data reported in the WHO 2014 Global Status Report on Alcohol and Health to evaluate associations between population drinking, cirrhosis cofactors, and economic indicators and the burden of alcoholic cirrhosis.

Materials and methods

Database development

We obtained detailed data on 193 countries from the WHO Global Information System on Alcohol and Health, accessed July, 2014 (<http://apps.who.int/gho-data/node.main.GISAH?lang=en>). From this data repository, we abstracted country-specific data on levels of alcohol consumption, drinking patterns, and our main outcome variables: the fraction of cirrhosis attributable to alcohol use (alcohol-attributable fraction, AAF), and the age-standardized death rate from cirrhosis (ASDR). The WHO collected data through household surveys, primarily the WHO global survey on alcohol and health, which was last conducted in 2012 in collaboration with all WHO regional offices and the European Commission. Prevalence data on potentially predisposing factors for cirrhosis, including cigarette smoking and obesity, were abstracted from the WHO Global Health Observatory (<http://www.who.int/gho/en/>). For hepatitis C virus (HCV) and B (HBV) virus seroprevalence, we obtained published data from systematic reviews of studies reporting HBV and HCV infection [25,26]. Data on per capita gross domestic product (GDP) were extracted from the World Bank (<http://data.worldbank.org/>).

Parameters on cirrhosis burden and potential determinants

Our primary outcome was the AAF of cirrhosis, the proportion of cirrhosis attributable to alcohol use in each country. The WHO derived this value using relative risk functions of cirrhosis for alcohol consumption in former and current drinkers. The mathematical definition is provided as Supplementary Fig. 1. The secondary outcome of cirrhosis mortality was assessed through the ASDR. Death rates were standardized to account for differences in age distributions across populations to make values comparable. As potential determinants of AAF and ASDR, we considered the following variables: average daily drinking among drinkers; annual per capita consumption of alcohol; type of alcohol (wine, beer, spirits, other); heavy episodic drinking (consumption of 60 g or more of pure alcohol on at least one occasion in the last 30 days); obesity (body mass index (BMI) of 30 kg/m² or greater); prevalence of cigarette smoking; seroprevalence of HCV and HBV; and GDP. We classified countries by heavy or moderate daily drinking based on guidelines from the U.S. Department of Agriculture [27]. The guidelines state that >2 standard drinks per day for men and >1 standard drink per day for women is considered heavy drinking. In the US, one standard drink contains roughly 14 g of

pure alcohol, which can be found in 350 ml (12 oz.) of beer (5% alcohol), 150 ml (5 oz.) of wine (12% alcohol), or 45 ml (1.5 oz.) distilled spirits (40% alcohol) [28]. We applied these guidelines to the population level, defining 21 g/day or greater of daily consumption as heavy drinking (1–2 standard drinks per day across men and women). Henceforth, this country classification will be referred to as the “daily intake designation”. Recognizing that other classifications to define heavy drinking exist, we performed an exploratory analysis with other published cut-off points (Supplementary Tables 4 and 5). To consider annual consumption, we converted data expressed in liters/year to standard drinks per/year using the conversion of 71.4 standard drinks per liter. In standard drinks, 1.5 drinks/day corresponds to 547 drinks/year and 7.7 liters/year. To assess GDP, countries were stratified according to the World Bank income categories of gross national income (low income: \$1,045, lower-middle: \$1,046–\$4,125, upper-middle: \$4,126–\$12,745, high-income: >\$12,745). Supplementary Table 1 describes all variables included in the database and their sources.

Statistical analysis

Global patterns in AAF and ASDR were examined by comparing mean values across the WHO Global Burden of Disease regional classifications (African region, region of the Americas, Eastern Mediterranean region, European region, South-East Asian region, and Western Pacific region; <http://www.who.int/choice/demography/regions/en/>). When appropriate, USA and Canada were considered separately as high-income North America, and Eastern Europe was considered separately from Europe. We performed multiple imputation, in order to take advantage of the full data set for the regression analyses (described in the Supplementary materials and methods). We conducted exploratory univariate linear regression analyses to investigate the potential individual association between each parameter and AAF and ASDR. Parameters that showed a significant association in the univariate analysis were included in a multivariate linear regression model. Comparisons between study groups were performed by Student's *t* test or Chi-squared test when appropriate, and Pearson coefficients were used for regressions. Data were analyzed using the IBM SPSS Statistics 21 statistical package, and *p* < 0.05 was considered to be statistically significant.

Results

Geographical variation in alcohol consumption, cirrhosis mortality and contribution from alcohol

We first analyzed the geographical patterns of alcohol consumption and cirrhosis mortality. The characteristics of the global cirrhosis burden and its potential determinants are described in Table 1. On a per capita basis, the highest alcohol consumption was observed in Europe with 10 liters/year (3677 standard drinks/year). In contrast, the rate was 1.1 liters/year (79 standard drinks/year) in the Eastern Mediterranean. There, an average of 6.5% of the population reported drinking, in contrast to 66% reported in Europe. When considering alcohol intake among those who drink, the average daily consumption ranged from 24 g per day in the Western Pacific region to 36 g in the African region.

The pattern of geographical variation in the percent of cirrhosis attributable to alcohol use (AAF) differed from all-cause cirrhosis mortality (Fig. 1A). The AAF rates were highest in the regions of USA/Canada and Europe, suggesting that in wealthier countries, alcohol makes a larger contribution to cirrhosis than in developing countries. The AAF values were: 62 in USA/Canada; 60 in Europe; 53 in Latin America; 50 in the Western Pacific; 48 in Africa; 33 in South-East Asia; and 14 in the Eastern Mediterranean. Notably, a significantly higher percent of cirrhosis is attributable to alcohol in Eastern Europe compared to Europe as a whole, with 67% in Eastern Europe. Fig. 2 presents AAF patterns in world map form.

Cirrhosis mortality (assessed through ASDR) was shown to vary significantly by region (Fig. 1B). In deaths per 100,000 within

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