

WJG 20th Anniversary Special Issues (11): Cirrhosis**Influence of unrecorded alcohol consumption on liver cirrhosis mortality**

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Abstract

Unrecorded alcohol includes illegally distributed alcohol as well as homemade or surrogate alcohol which is unintended for consumption by humans (*e.g.*, cosmetics containing alcohol). The highest unrecorded alcohol consumption occurs in Eastern Europe and some of these countries have an over proportional liver cirrhosis mortality. Compounds besides ethanol have been hypothesized as being responsible for this observation. On the other hand, chemical investigations were unable to prove that unrecorded alcohol regularly contains contaminants above toxicological thresholds. However, illegally produced spirits regularly contain higher per-

centages of alcohol (above 45% by volume), but for considerably less costs compared with licit beverages, potentially causing more problematic patterns of drinking. In this review, it is investigated whether patterns of drinking rather than product composition can explain the liver cirrhosis mortality rates. Statistical examination of World Health Organization country data shows that the originally detected correlation of the percentage of unrecorded alcohol consumption and liver cirrhosis mortality rates disappears when the data is adjusted for the prevalence of heavy episodic drinking. It may be concluded that there is currently a lack of data to demonstrate causality between the composition of illicit spirits (*e.g.*, higher levels of certain contaminants in home-produced products) and liver toxicity on a population scale. Exceptions may be cases of poisoning with antiseptic liquids containing compounds such as polyhexamethyleneguanidine, which were reported to be consumed as surrogate alcohol in Russia, leading to an outbreak of acute cholestatic liver injury, histologically different from conventional alcoholic liver disease.

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Key words: Epidemiology; Liver cirrhosis; Alcoholic beverages; Unrecorded alcohol; Risk assessment

Core tip: Various constituents and contaminants of unrecorded alcohol (*i.e.*, illicitly or informally produced alcohol) were implicated as over proportionally causing liver disease. Quantitative risk assessments were not able to corroborate these claims by identifying such contaminants above toxicological levels, however. The higher rates of liver disease can be alternatively explained by more detrimental patterns of drinking in regions with a high prevalence of unrecorded alcohol consumption.

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INTRODUCTION

In Central and Eastern Europe, large discrepancies can be found between recorded alcoholic beverage consumption and alcohol-related mortality^[1]. An example is Hungary, a country in which liver disease mortality is circa four times that of countries with comparable per capita consumption of alcohol (*e.g.*, Refs.^[2,3]). An explanation for this finding might be the particularly high unrecorded alcohol consumption^[2].

Despite the high levels of unrecorded alcohol consumption in some countries (up to 40% of total consumption), there is an absence of data about chronic long-term health consequences that may specifically be influenced by unrecorded alcohol consumption. The proof of causality is particularly difficult because people may co-consume both forms of alcohol (*i.e.*, recorded and unrecorded alcohol)^[4]. Rehm *et al*^[4] have provided an example of a Russian person having died of alcoholic liver cirrhosis, and for whom unrecorded alcohol products were the main form of alcohol consumption in his final years. Nevertheless, he would have been expected to exclusively consume recorded alcohol for some years before switching out of economic reasons to unrecorded alcohol consumption (typically to medicinal, cosmetic or other surrogate alcohol) when his patterns of drinking became more and more detrimental^[5]. With this change and the following exposure to “other” forms of alcohol, there are 3 potential effects according to Rehm *et al*^[4]: “(1) The alcoholic liver cirrhosis would have taken exactly the same course; (2) The alcoholic liver cirrhosis would have taken a different course, for example, later onset, longer duration, or no fatal outcome, if this person had consumed recorded alcohol only; and (3) The alcoholic liver cirrhosis would not have occurred with consumption of recorded alcohol”.

The determination of causality of the link of unrecorded alcohol with chronic disease is, therefore, a challenging task^[6,7]. As a result, few studies have researched the question if unrecorded alcohol consumption may have detrimental health effects that are not found in recorded consumption, *e.g.*, because unrecorded alcohol may contain some compounds that are not present in recorded alcohol. An exception is a study from India^[8], which found an association between unrecorded alcohol consumption (country liquor) and an increased risk of alcoholic liver disease, particularly alcoholic liver cirrhosis. It is notable that the country liquor contained lower alcoholic strengths than the local types of recorded alcohol. However, the study may have been confounded by social status and other factors that were not well controlled^[4].

The connection between unrecorded alcohol consumption levels and liver cirrhosis mortality rates can be

inferred from Figure 1. Hungary, Moldova and Romania show very high levels of unrecorded adult (15+) per capita alcohol consumption [4.0 L (Hungary, Romania) or 10 L (Moldova) of pure alcohol per year]. For these countries, liver cirrhosis mortality rates (47, 43 and 119 per 100000 adult population for Hungary, Romania and Moldova, respectively) were much higher than for other European countries. In contrast, comparably low unrecorded alcohol consumption in France, Spain, and Switzerland (0.34, 1.4, and 0.50 L of pure alcohol per year) were associated with low liver cirrhosis mortality rates in these countries (less than 12 deaths per 100000 adult population from alcoholic liver disease).

INVESTIGATION INTO THE INFLUENCE OF UNRECORDED ALCOHOL CONSUMPTION ON LIVER CIRRHOSIS MORTALITY

To provide further and more systematic insight into the connection between unrecorded alcohol consumption and liver cirrhosis, the following data was taken from the Global Information System on Alcohol and Health (GISAH) of the World Health Organization (WHO)^[9]: (1) The liver cirrhosis age-standardized mortality rate is “the number of individuals in a given population (100000 people) that died from alcoholic liver disease during a calendar year (2005)”. Only adults (population above 15 years) were taken into account; (2) The levels of unrecorded and total consumption (in liters of pure alcohol) for the year 2005 and for the population older than 15 years; and (3) Heavy episodic drinkers, defined as “the percentage of adults (aged 15+) who have drunk at least 60 g (approximately 6 standard alcoholic drinks) or more of pure alcohol on at least one occasion weekly”.

The following definitions are quoted verbatim from the WHO GISAH website^[9] for reasons of clarity: “recorded alcohol consumption refers to official statistics (production, import, export, and sales or taxation data), while unrecorded alcohol consumption refers to alcohol which is not taxed and is outside the usual system of governmental control, such as home- or informally-produced alcohol (legal or illegal), smuggled alcohol, surrogate alcohol (which is alcohol not intended for human consumption), or alcohol obtained through cross-border shopping (which is recorded in a different jurisdiction). Recorded adult per capita consumption of pure alcohol is calculated as the sum of beverage-specific alcohol consumption of pure alcohol (beer, wine, spirits, other) from different sources. The first priority in the decision tree is given to government statistics; second are country-specific alcohol industry statistics in the public domain (Canadian, IWSR-International Wine and Spirit Research, OIV-International Organisation of Vine and Wine, Wine Institute, historically World Drink Trends); and third is the Food and Agriculture Organization of the United Nations’ statistical database (FAOSTAT). The method of

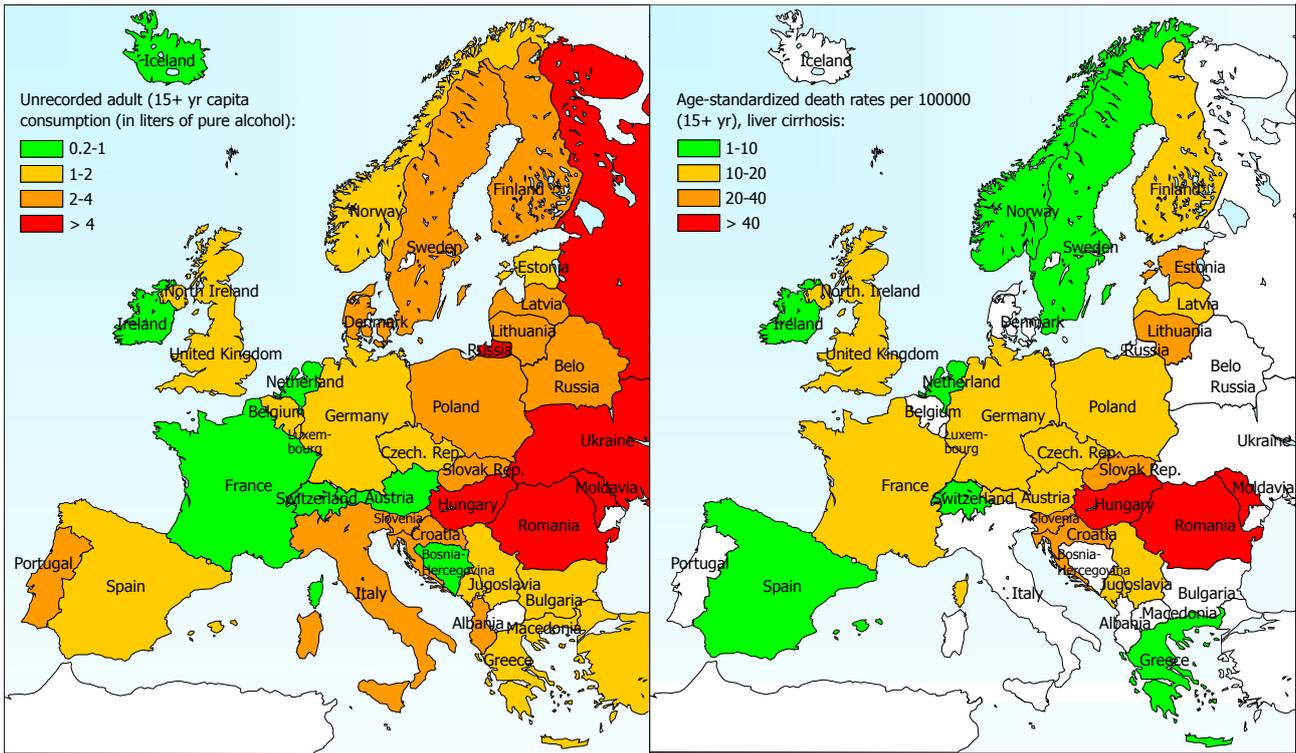


Figure 1 Comparison of levels of unrecorded alcohol consumption and liver cirrhosis mortality rates in Europe for 2005. Data from World Health Organization^[9]; no data available for uncolored countries.

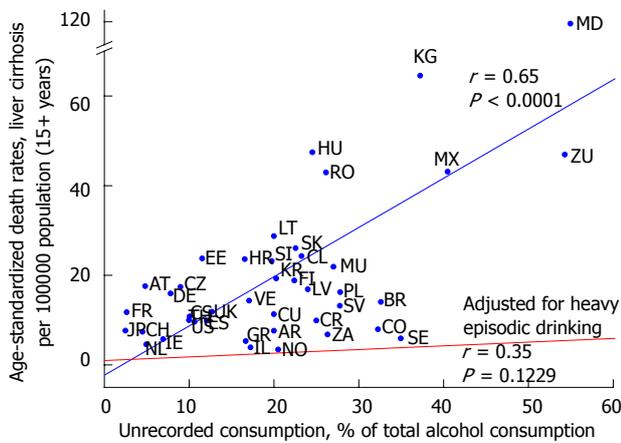


Figure 2 Correlation between unrecorded alcohol consumption and liver cirrhosis mortality for countries worldwide. Own calculation based on World Health Organization data^[9]; the lower curve shows the result after controlling for heavy episodic drinking.

measurement of unrecorded alcohol consumption gives the first priority in the decision tree to nationally representative empirical data; these are often general population surveys in countries where alcohol is legal. Second are specific other empirical investigations, and third is expert opinion. Survey questions on consumption of unrecorded alcohol are converted into estimates per year of unrecorded adult per capita consumption. Usually surveys underestimate consumption. However, in countries where survey based estimates exceeded the recorded

consumption, unrecorded was calculated as total consumption estimated from survey minus recorded adult per capita consumption. In some countries, unrecorded is estimated based on confiscated alcohol confiscated by customs or police. Total consumption is the sum of recorded and unrecorded consumption²⁷.

The full methodology is available on the WHO GISAH webpages^[9,10]. The percentage of unrecorded alcohol consumption for each country was then calculated from these data.

Data analysis was conducted with Origin V.7.5 (Originlab, Northampton, United States). Mathematical correlation between the investigated parameters was evaluated using linear regression for all countries for which data was available. The 0.05 probability level was used to define statistical significance. The results are shown in Figure 2.

There appears to be a statistically significant correlation between mortality from liver cirrhosis and the amount of unrecorded alcohol consumption ($r = 0.65$, $P < 0.0001$). This trend upholds even when the data is controlled for per capita consumption ($r = 0.35$, $P = 0.04$; for calculation see Ref.^[11]), but becomes non-significant after controlling for heavy episodic drinking ($r = 0.35$, $P = 0.12$). However, five countries (Hungary, Estonia, Slovakia, Mauritius, and Ecuador) still showed over proportional liver cirrhosis mortality after the adjustment for heavy episodic drinking. However, as consumption of alcohol *per se* may also cause liver cirrhosis, it remains unclear what the specific contribution of unrecorded al-

Table 1 Compounds potentially associated with toxicity in unrecorded alcohol

Compounds in unrecorded alcohol	Occurrence	Toxic effect	Risk assessment
Ethanol	Main components of every alcoholic beverage; often found in higher strength in unrecorded alcohols	Several acute and chronic health effects including liver cirrhosis	Major risk factor of unrecorded alcohol on a population scale
Methanol	Minor constituent in all alcoholic beverages, higher in some fruit spirits; acute toxic concentrations due to adulteration	Poisoning at high concentrations	Extremely high risk for consumers of highly contaminated products; poisoning outbreaks are uncommon but cause high morbidity/mortality
Higher alcohols (e.g., propanol, butanol)	Minor constituents in all alcoholic beverages, higher concentrations in certain fruit spirits	Similar to ethanol	Lack of causality with effects of unrecorded alcohol (exposure below thresholds)
Acetaldehyde	Minor constituents in all alcoholic beverages, higher concentrations in certain fruit spirits	Carcinogenicity	Could constitute higher chronic risk if contained at higher levels, but epidemiological evidence is missing
Ethyl carbamate	High levels in stone fruit spirits	No human data. Hepatocellular tumors in rodents	See acetaldehyde
Diethyl phthalate	Denatured alcohols	Developmental effects, hepatotoxicity in animals	See acetaldehyde
Coumarin	Flavoring in cosmetic alcohol	Hepatotoxicity in animals	See acetaldehyde
Polyhexamethyleneguanidine	Antiseptic liquids in Russia	Potentially causing cholestatic hepatitis in humans	Unclear causality, but observational studies suggest a plausible risk

cohol may be^[11,12].

MECHANISMS POTENTIALLY LEADING TO OVER PROPORTIONAL LIVER CIRRHOSIS MORTALITY ASSOCIATED WITH UNRECORDED ALCOHOL CONSUMPTION

The large variance of cirrhosis mortality rates between the countries Hungary and Romania and the rest of Europe, mentioned above, were suggested to having been caused by some specific compounds in unrecorded alcoholic beverages^[2] but not by differences in drinking behavior between recorded and unrecorded alcohol (e.g., regarding the volume or patterns of consumption)^[13,14].

Some studies (see summary in Refs.^[12,15]) have used various chemical methods to systematically analyze the composition of unrecorded alcoholic beverages with the focus on potential harmful components (Table 1). If we examine the potential long-term health consequences of unrecorded alcohol consumption such as liver cirrhosis, a single consistent finding was regularly described: the concentration of ethanol is higher in unrecorded alcohols (considerably above 40% vol) than in the recorded alcoholic beverages^[4]. These higher contents of ethanol alone may cause detrimental effects, for example, regarding injuries and ethanol intoxication. The alcoholic strength of unrecorded alcohol is normally not labeled, so that the consumer is unaware that some high strength types should be diluted with water before consumption. Therefore, the original high-strength beverages could be consumed directly^[12].

Other components besides ethanol analyzed in unrecorded alcohols were below toxicological thresholds in

most of the samples^[15-17]. For example, some hepatotoxic contaminants such as copper or ethyl carbamate were found in some samples of unrecorded alcohol, however, the intake in alcohol consumers was below 1% of the threshold doses in rodents^[16]. In conclusion, there are considerable research needs regarding unrecorded alcohol^[18]. In light of the current state of research, the authors believe that the two indicators “volume of alcohol consumption” and “drinking patterns” are the major contributors that cause the observed differences in liver cirrhosis mortality^[16]. Both indicators may be influenced by unrecorded alcohol because it typically contains higher concentrations of ethanol and its lower costs may additionally increase the drinking amounts^[16]. Unrecorded alcohol consumption is also inversely associated with socioeconomic status (SES) and education, both of which are also factors connected to alcohol-related death, disease and injury^[19]. Further confounding factors in the population consuming unrecorded alcohol may be drug use, viral hepatitis or HIV, which could potentially contribute to multifactorial liver disease^[12]. However, there is currently an absence of quantitative epidemiological research on these risk factors in connection with unrecorded alcohol consumption.

METHANOL AND PHMG: EXCEPTIONS TO THE RULE

While unrecorded alcohol seldom contains substances more toxic than ethanol itself, the exception to the rule may be isolated outbreaks of methanol poisoning^[20] as well as the occurrence of polyhexamethyleneguanidine hydrochloride (PHMG). PHMG is a substance that was linked to widespread acute cholestatic liver injury in Russia connected to the consumption of surrogate

alcohol^[21]. In that case, the surrogate that was ingested was an antiseptic fluid, which consisted of ethanol (93%), diethyl phthalate (DEP) (0.08%-0.15%) and PHMG (0.10%-0.14%). While PHMG is the disinfecting ingredient^[22], DEP is used to denature the alcohol^[23]. Several other Russian studies detected PHMG together with DEP in solutions consumed as surrogate alcohol connected to intoxications^[6,22,24]. Ostapenko *et al.*^[21] concluded from clinical and laboratory findings in 579 cases that the cholestatic hepatitis histologically different from conventional alcoholic liver disease was connected to PHMG exposure. A history of hepatitis and cirrhosis caused by long-term alcohol consumption may have contributed to a more severe course of the intoxication. Besides PHMG, multifactorial liver damage may have been caused by further factors such as DEP or chronic viral hepatitis. Nevertheless, the causality in these poisoning cases in Russia remains questionable because the exact composition of the surrogate alcohol that has been consumed is often unknown, and the studies were not controlled for confounding factors such as volume and patterns of drinking^[12,17,25].

CONCLUSION

Comprehensive literature reviews proof that concerns about the health effects of unrecorded alcohol were typically overstated^[4,15]. To provide only one example, the first quantitative risk assessments of compounds in alcohol have provided evidence that the effect of alcohol itself regarding harm to the liver is more than 5000 times greater than the one of ethyl carbamate^[26,27]. Liver cirrhosis mortality rates connected to unrecorded alcohol consumption may be rather explained by the higher ethanol contents, detrimental patterns of drinking, lower SES and poor health status and the interaction between these indicators than by reference to alcohol quality^[4].

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