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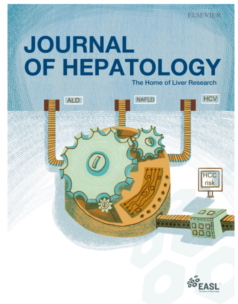

Association between public health policies on alcohol and worldwide cancer, liver disease and cardiovascular disease outcomes

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Association between public health policies on alcohol and worldwide cancer, liver disease and cardiovascular disease outcomes

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ABSTRACT

Background & Aims: The long-term impact of alcohol-related public health policies (PHP) on disease burden is unclear. We aimed to assess the association between alcohol-related PHP and alcohol-related health consequences.

Methods: Ecological multi-national study including 169 countries. We collected data on alcohol-related PHP from the WHO Global Information System of Alcohol and Health 2010. Data on alcohol-related health consequences between 2010–2019 were obtained from the Global Burden of Disease database. We classified PHP into five items, including criteria for low, moderate, and strong PHP establishment. We estimated an alcohol preparedness index (API) using multiple correspondence analysis (0 lowest and 100 highest establishment). We estimated an incidence rate ratio (IRR) for outcomes according to API using adjusted multilevel generalized linear models with a Poisson family distribution.

Results: The median API in the 169 countries was 54 [IQR:34.9–76.8]. The API was inversely associated with alcohol use disorder prevalence (AUD)(IRR:0.13, 95%CI:0.03–0.60; p=0.010), alcohol-associated liver disease (ALD) mortality (IRR:0.14 95%CI:0.03–0.79; p=0.025), mortality due to neoplasms (IRR:0.09, 95%CI:0.02–0.40; p=0.002), alcohol-attributable hepatocellular carcinoma (HCC) (IRR:0.13, 95%CI:0.02–0.65; p=0.014), and cardiovascular diseases (IRR:0.09, 95%CI:0.02–0.41; p=0.002). The highest associations were observed in the Americas, Africa, and Europe. These associations became stronger over time, and AUD prevalence was significantly lower after 2 years, while ALD mortality and alcohol-attributable HCC incidence decreased after 4 and 8 years from baseline API assessment, respectively ($p<0.05$).

Conclusions: The API is a valuable instrument to quantify the robustness of alcohol-related PHP establishment. Those countries with a higher API were associated with lower AUD prevalence, ALD mortality, neoplasms, alcohol-attributable HCC, and cardiovascular diseases. Our results encourage the development and strengthening of alcohol-related policies worldwide.

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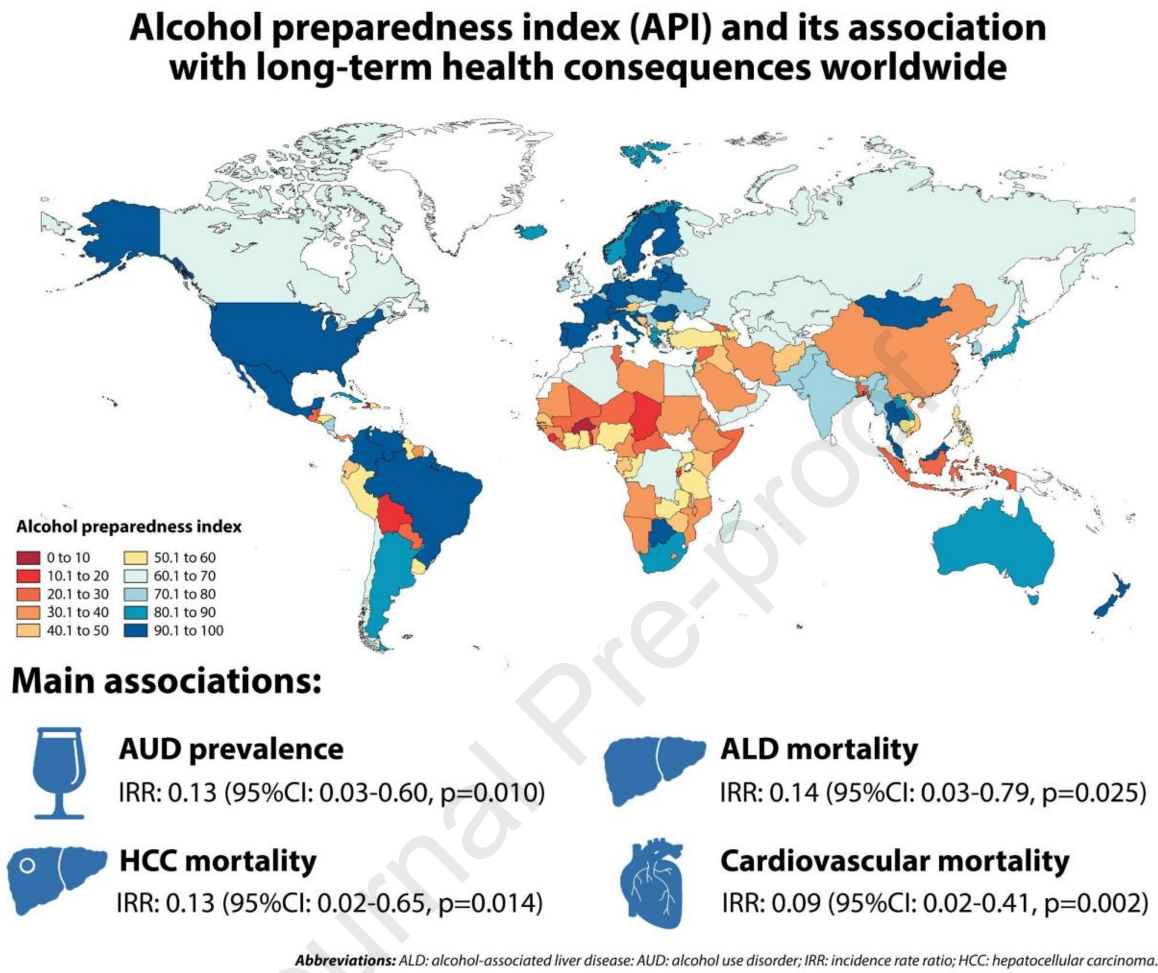
IMPACT AND IMPLICATIONS

- We first developed the *Alcohol Preparedness Index* (API), an instrument to assess the existence of alcohol-related public policies for each country. We then evaluated the long-term association of the country's API in 2010 with the burden of chronic liver disease, hepatocellular carcinoma, other neoplasms, and cardiovascular disease.

- The strengthening of alcohol-related public health policies could impact long-term mortality rates from cardiovascular disease, neoplasms, and liver disease, These conditions are the main contributors to the global burden of disease related to alcohol use. Over time, this association has not only persisted but also grown stronger.

- Our results expand the preliminary evidence regarding the importance of public health policies in controlling alcohol-related health consequences.

GRAPHICAL ABSTRACT



INTRODUCTION

Alcohol consumption is an important risk factor for illness, disability, and mortality [1,2]. Alcohol especially affects young and middle-aged individuals in their prime working years compared to other risk factors, with a peak age of death occurring in the late 40s and early 50s [3]. The most striking health consequences of alcohol consumption are liver diseases, such as cirrhosis, hepatocellular carcinoma (HCC), and alcohol-associated hepatitis (AH) [4–6]. Moreover, alcohol intake has been strongly associated with several types of non-liver neoplasms, trauma, cardiac disease, and psychiatric disorders, among others [7]. Based on the available evidence, the safest alcohol dose to minimize health consequences should be maybe close to zero, especially in young adults [1]. Alcohol abstinence can also decrease mortality and disability-adjusted life years (DALYs), and constitutes one of the best predictors of survival in ALD and AH [8].

Preventable measures to reduce alcohol consumption, early identification of those at risk, and widely available treatments for alcohol use disorder (AUD) are essential to decrease the burden of liver disease [3,9]. Multiple studies have shown that implementing public health policies may reduce alcohol intake and road traffic injuries [9]. However, studies on the impact of alcohol-related public health policies on long-term outcomes, such as ALD or HCC, are scarce. Our recent study in Latin America demonstrated that the establishment of alcohol-related PHP is strongly associated with lower AUD prevalence and mortality due to ALD [2]. However, the influence of global social, cultural, ethnic, and economic differences could impact each policy's usefulness and overall reach [10]. In addition, the long-term effect of alcohol-related PHP on several health consequences, including neoplasms and cardiovascular disease, is unknown. In this study, we aimed to develop an instrument to quantify the establishment of policies on alcohol in each country aligned with the World Health Organization (WHO) SAFER initiative, and to assess the relationship between the establishment of alcohol-related PHP and the burden of alcohol-related health consequences in the long-term.

METHODS

Study Design and participant countries

We conducted an ecological multi-national study worldwide. We registered the presence of alcohol-related PHP in each country enforced in 2010 (**Supplementary Table 1**). Data were also obtained from the WHO Global Information System of Alcohol and Health (GISAH). Three independent investigators collected all the data (MC, DV, and AM), and disagreements were resolved by a fourth reviewer (MPM). Policies were categorized according to the 2018 WHO classification [11]. We excluded 24 countries that did not have complete information on PHP (**Supplementary Table 2**). All the information was aggregated at a country level, and we relied on publicly available data. Therefore, this study was considered exempt from ethics review by the *Pontificia Universidad Católica de Chile* institutional review board (ID: 230304001).

The socio-demographic information was collected from the World Bank Open Data source (http://databank.worldbank.org). Data on alcohol consumption measures and their harmful health consequences in each country were collected from the WHO GISAH and the Global Burden of Disease (GBD) databases (between 2010 and 2019)[12]. We included the alcohol per capita consumption (APC) in liters of pure alcohol per year and the prevalence of AUD (including alcohol dependence and harmful use of alcohol), according to the *Diagnostic and Statistical Manual of Mental Disorders, fifth edition.* Thus, we gathered information on outcomes related to the disease burden due to alcohol, and all outcomes were registered annually from 2010 to 2019 (**Supplementary Tables 3–12**)[12]. This study adheres to the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) statement [13].

We generated an instrument to address the establishment of PHP on alcohol among countries. The development phases of this instrument are detailed in **Supplementary Methods.** This instrument was constructed by a group of Hepatology and Public Health experts using three different sources: the WHO GISAH data, the WHO SAFER initiative, and preliminary evidence on best buy policies. As a result, we obtained a 5-item instrument: 1. National policy to fight harmful consequences of alcohol; 2. Control over production, pricing, and taxes; 3. Marketing of alcoholic beverages and restrictions to alcohol access; 4. Drink-driving policies and countermeasures; 5. Monitoring and surveillance. All the policies available in the WHO GISAH were used as measurements and included in the five items (**Table 1 and Supplementary Table 13**). Subsequently, we defined criteria for a low, moderate, and strong establishment of policies (**Supplementary Methods**). All the research team evaluated the proposed instrument using an estimate-talk-estimate modified Delphi method, and all the participants fully agreed with the final version [14].

Outcomes

The main outcomes were directly associated with alcohol misuse, including age-standardized AUD prevalence, mortality due to ALD, and alcohol-attributable hepatocellular carcinoma (HCC) incidence and mortality between 2010 and 2019. Secondary outcomes comprised other conditions related to alcohol consumption, including age-standardized mortality due to cirrhosis (including all causes), mortality due to neoplasms (including all causes), cardiovascular mortality, and prevalence of alcohol-associated cardiomyopathy (ACMP) between 2010 and 2019. A description of estimation methods by the GBD group is available in **Supplementary Methods**.

Statistical analysis

We used multiple correspondence analysis (MCA) to estimate an Alcohol Preparedness Index (API) for each country based on the scores obtained from the 5-item instrument [15]. MCA identifies composite dimensions in datasets consisting of categorical variables (i.e., the strength of alcohol-related PHP in each item). This approach combines all the information observed in the categorical values for the 5-item instrument into a single factor that acts as a weighted summary of each possible different level indicator combination for each country. The full description of MCA is available in the **Supplementary Methods**. The weighted summary has an assigned weight for each individual level of indicator, which combines to give the full score of the country (**Supplementary Table 13**). We standardized the obtained indicator in order to be able to compare the performance among countries easily. Thus, the API ranged from 0 to 100, being 0 the lowest preparedness and 100 the highest.

To assess the association between the API and disease burden outcomes, we built multilevel generalized linear models (GLM) with a Poisson family distribution, log link, and a robust variance estimator. Multilevel models with a random intercept were run to analyze differences in consecutive years of each country (2010 to 2019). Using these models, we estimated an adjusted incidence rate ratio (IRR). To correctly account for the country population's size differences, a predictor term called offset (natural logarithm of the population's size), was incorporated into the model. We adjusted the models by age structure using the proportion of individuals aged 15–64 years per country, Human Development Index, Healthcare Access and Quality index, and gross domestic product (GDP) on a logarithmic scale. Subsequently, we introduced an interaction term between the API and time to assess the relationship over time. As a sensitivity analysis, we assessed the association between API and AUD incidence, ALD prevalence, and DALYs due to ALD. In models assessing quartiles, we added a cubic function to models, since the linear trend breaks up at the third and fourth quartiles. We also assessed a falsification endpoint (age-related hearing loss) to ensure that associations were unrelated to other socioeconomic variables. The **Supplementary Methods** contain an in-depth description of the models used in this study. The analyses were performed with STATA software version 17 (StataCorp, College Station, Texas), and a p-value <0.05 was considered statistically significant.

Role of the funding source

Funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript.

RESULTS

A total of 169 countries were included (50 from Africa, 35 from the Americas, 33 from Asia, 46 from Europe, and 5 from Oceania). According to the World Bank classification, there were 26 (15.6%) low-income countries, 44 (26.4%) lower-middle countries, 47 (28.1%) upper-middle countries, and 50 (29.9%) high-income countries. The estimated GDP per capita was $US 6,109 [IQR 1,725-17,448] and the median Gini index was 36.8 [IQR 32.8-43.3] in 2019. At least 39.4% [IQR 26.1-65.4%] of individuals over 15 years old were current drinkers. The worldwide APC in those over 15 years old reached 6.6 [IQR 2.8-9.7] liters of pure alcohol, including 4.7 [IQR 1.7-8.0] and 1.2 [IQR 0.6-2.0] liters of recorded and unrecorded consumption, respectively. The main baseline characteristics of each continent are summarized in **Table 2**.

Globally, the existence of PHP on alcohol was weak, and less than a third of countries have developed strong policies in each dimension (**Table 3**). Indeed, the presence of a national plan and control over marketing and restrictions on alcohol access often had a low establishment level (59.2% and 38.5%, respectively). The other three dimensions scored mainly in the moderate establishment level (drunk-driving policies 72.2%, control over production, pricing and taxes 59.8%, and monitoring and surveillance 38.5%). In 2016, only ten countries established a minimum unit pricing (MUP) policy, including Canada, Central African Republic, Democratic Republic of the Congo, Kazakhstan, Russian Federation, Slovakia, Timor-Leste, Ukraine, United

Kingdom, and Uzbekistan. The regional differences between continents are summarized in **Table 3**.

The API was obtained based on the MCA estimation, ranging from 0 to 100 (**Figure 1**). The median API was 54 [IQR 34.9-76.8] (**Table 2**). We observed that the highest contributions to the index were due to monitoring and surveillance, and a national policy to fight harmful consequences of alcohol items (**Supplementary Table 14**). Europe achieved the highest score with 77 [IQR 54.4-93.7], while Africa had the lowest score with 39.1 [IQR 28.5-52.9] (**Table 3**). Indeed, 56.1% of countries in the highest percentile were European (**Supplementary Table 14**). The highest-scoring countries were Brazil, Cyprus, Latvia, Malaysia, Netherlands, Poland, Portugal, Spain, and the United States, scoring 100. On the other side, Bolivia (12.3), Burundi (12.3), Togo (10.1), Antigua and Barbuda (4.1), Burkina Faso (0), Haiti (0), Niue (0), and Sao Tome and Principe (0) obtained the lowest score (**Figure 1**).

The median AUD prevalence was 1.6% [IQR 0.8-2.3%] in 2019 (**Supplementary Table 3**). A higher number of policies was associated with a lower AUD prevalence (IRR 0.76, 95%CI 0.63-0.91; p=0.004) (**Supplementary Table 15**). The API also showed a statistically significant association between higher preparedness and lower AUD prevalence (IRR 0.13, 95%CI 0.03-0.60; p=0.010)(**Figure 2A**). In particular, the API in the Americas region strongly correlated with AUD prevalence (**Supplementary Table 17**). Although Europe did not have a linear association, a subgroup analysis comparing quartiles showed a statistically significant non-linear association, which was higher in the second, third, and fourth quartiles (**Supplementary Table 18**).

The estimated mortality rate due to cirrhosis was 20.9 [IQR 11.6–34.1] per 100,000 inhabitants in 2019, and a total of 6.4 [IQR 3.9–8.9] individuals per 100,000 inhabitants died due to ALD in the same period (**Supplementary Tables 4–5**). A higher number of policies was associated with lower mortality due to cirrhosis (IRR 0.80, 95%CI 0.66-0.97; p=0.021) and ALD (IRR 0.77, 95%CI 0.63-0.95; p=0.016)(**Supplementary Table 15**). Also, a higher API correlated with lower mortality due to cirrhosis (IRR 0.12, 95%CI 0.03-0.56; p=0.007) and ALD (IRR 0.14 95%CI 0.03-0.79; p=0.025)(**Figure 2B-C**). Africa and the Americas exhibited the strongest association between policies and lower ALD mortality, while Europe had a non-linear association (**Supplementary Tables 17–18**).

The estimated mortality due to neoplasms (including all causes) was 123.0 [IQR 108.4-144.8] cases per 100,000 inhabitants in 2019 (**Supplementary Table 6**). The establishment of alcohol-related PHP and the API were associated with lesser deaths due to neoplasms (IRR 0.75, 95%CI 0.63-0.89; p=0.001 and IRR 0.09, 95%CI 0.02-0.40; p=0.002, respectively)(**Figure 2D, Supplementary Tables 15–16**). The incidence and mortality of alcohol-attributable HCC were 1.0 [IQR 0.7–1.6] and 1.1 [IQR 0.7–1.5] cases per 100,000 inhabitants in 2019, respectively (**Supplementary Tables 7–8**). There was a statistically significant association between the establishment of alcohol-related PHP and alcohol-attributable HCC incidence (IRR 0.76, 95%CI 0.63-0.93; p=0.006) and mortality (IRR 0.76, 95%CI 0.63-0.93; p=0.006)(**Supplementary Table 15**). Furthermore, the API also was associated with a lower alcohol-attributable HCC incidence (IRR 0.13, 95%CI 0.02-0.66; p=0.015) and mortality (IRR 0.13, 95%CI 0.02-0.65; p=0.014)(**Figures 2E-F**). Africa and the Americas had a statistically significant association between the API and the burden of alcohol-attributable HCC, while Europe also had a non-linear association (**Supplementary Tables 17–18**).

Cardiovascular diseases are a major cause of mortality worldwide, with an estimated mortality rate of 269.0 [IQR 183.9-343.6] cases per 100,000 inhabitants in 2019 (**Supplementary Table 9**). In addition, the ACMP prevalence was 3.6 [IQR 1.6–8.6] per 100,000 inhabitants for the same period (**Supplementary Table 10**). The alcohol-related PHP and the API were associated with lower cardiovascular mortality (IRR 0.78, 95%CI 0.65-0.92; p=0.009, and IRR 0.09, 95%CI 0.02-0.41; p=0.002, respectively)(**Figure G, Supplementary Tables 15–16**). Both assessment methods also demonstrated an association with lower ACMP prevalence (IRR 0.70, 95%CI 0.56-0.89; p=0.004, and IRR 0.07, 95%CI 0.01-0.48; p=0.007, respectively)(**Figure H**). However, if we analyzed the regional differences, Africa and the Americas showed a statistically significant association between the API and lower cardiovascular mortality and ACMP prevalence (**Supplementary Table 17**). Europe also showed a robust non-linear association when analyzed by quartiles (**Supplementary Table 18**).

We identified a significant interaction between the API and a decrease in alcohol-related outcomes over time, but the progression was different among outcomes. From API baseline in 2010, a significant association was observed after 2 years in AUD prevalence (**Figure 3**), 4 years in ALD mortality (**Figure 4**), and 3 years in cardiovascular mortality (**Supplementary Figure 1**). On the other side, this association was significant after 8 and 7 years in alcohol-attributable HCC incidence and mortality, respectively (**Supplementary Figures 2–3**), after 7 years in mortality due to cirrhosis (including all causes) (**Supplementary Figure 4**), 6 years in mortality due to neoplasms (**Supplementary Figure 5**), and around 6 years in ACMP prevalence (**Supplementary Figure 6**). In the sensitivity analyses, we assessed the relationship between API and AUD incidence, where interaction between time and API showed statistical significance, but seemed to diminish in the later years of follow-up. To explore this, we divided the API into quartiles (four groups) and observed that the decreasing trend in the incidence of AUD remained linear within the quartile representing the highest API values (fourth quartile) (**Supplementary Table 22**). API also exhibits an association with ALD prevalence over time, which was significant after 6 years of baseline API assessment (**Supplementary Figure 7**), especially in individuals aged 50 years or over and men (**Supplementary Table 23**). A significant association was also observed between API and DALYs due to ALD over time, particularly 3 years after baseline API assessment (**Supplementary Figure 8**). Finally, there was no association between API and age-related hearing loss during the entire period (IRR 0.99, 95%CI 0.99–1.01, p=0.791) and over time (**Supplementary Figure 9**).

DISCUSSION

In this study, we developed a 5-item instrument to quantify the establishment of alcohol-related PHP. Through this instrument, we created the alcohol preparedness index (API) to quantify the PHP's strength on alcohol. We demonstrated that: 1. The establishment of PHP on alcohol-related outcomes was heterogeneous; 2. Less than a third of countries achieved a strong establishment of PHP on alcohol for each dimension; 3. A higher API was associated with a lower burden of ALD, including AUD prevalence, ALD mortality, and alcohol-attributable HCC; 4. A better API was also associated with lower mortality due to neoplasms and cardiovascular disease; 5. The measures of association (incidence rate ratio) exhibited greater magnitude and enhanced precision in their confidence intervals in the models of alcohol-related outcomes stratified by Africa, the Americas, and Europe than in other regions; 6. API exhibits a significant and strong association with all the outcomes over time, but the progression seems to be different among outcomes.

The overall API provides insights into the national alcohol preparedness for each country, while the ranking allows for comparing performance between a country and the other nations included. The higher scores were obtained by strong monitoring and surveillance policies, and the presence of an adequate national policy on alcohol. Although establishing PHP is the cornerstone to decrease the long-term consequences of alcohol use, the interactions between different policies on alcohol and its burden are not well known. To our knowledge, only a few instruments have been made to assess the strength of alcohol-related PHP. Of note, the Alcohol

Control Policy Index (ACPI) has shown a correlation with alcohol use, but it has not been used to assess alcohol-related health consequences [16]. The Alcohol Policy Index is another tool to assess alcohol-related PHP which was used to explore the association with alcohol use among the Organization for Economic Cooperation and Development (OECD) countries, but it excluded relevant policies such as the presence of a national plan and monitoring systems [17]. The International Alcohol Control (IAC) policy index has been recently published and also correlates with alcohol intake, however, only policies on alcohol availability, pricing policies, alcohol marketing, and drink-driving policies were included [18]. A similar approach was made in the International Alcohol Policy and Injury Index (APII), which included only policies on physical availability, drinking context, pricing, advertising, and vehicular, showing a correlation with alcohol-attributable fractions for vehicular deaths [19]. Another prior study based on an instrument called Alcohol Policy Scale, showed that policies on alcohol were associated with lower binge-drinking consumption and ALD mortality, mainly focused on restrictions to alcohol access [20,21]. Of note, none of the existing indexes included policies to facilitate access to screening, brief interventions and treatment (a SAFER component). Thus, the API assessed the alcohol-related PHP existence from a comprehensive perspective, well-correlated with the prediction of long-term health consequences, is more aligned with the WHO SAFER initiative recommendations than other instruments, and was assessed over time (**Supplementary Table 24**).

Taxes and pricing policies are among the most successful PHP in decreasing alcohol intake and ALD. In fact, several studies have demonstrated an inverse association between taxes, alcohol consumption, and alcohol-related harmful effects [22]. This effect of taxes might mostly impact the middle-aged population and those with a low socioeconomic status [23]. Establishing a MUP is also a useful strategy to decrease heavy-episodic drinking and ALD mortality [24]. Still, its effectiveness could differ in other regions with a high homemade alcohol intake or illegal markets. Restrictions to alcohol access and control over ads also have important benefits on decreasing alcohol-attributable mortality, but only a few studies have assessed its effect on ALD [25].

At a population level, heavy alcohol intake is the main factor influencing the burden of cirrhosis and ALD per country, independently of the drinking pattern and type of alcoholic beverage [26,27]. In particular, alcohol misuse has been shown to impact various forms of liver disease, including Hepatitis B virus (HBV), hepatitis C virus (HCV), and metabolic dysfunction-associated steatotic liver disease [4]. For example, a modeling study in the USA suggested that alcohol use caused 1,700 acute HBV and HCV infections attributable to heavy-drinking occasions in 2017, while 14,000 chronic HBV and 1,700 chronic HCV infections could be attributed to heavy alcohol use interfering with spontaneous clearance [28].

Alcohol is a well-established carcinogenic for several malignancies, such as oral cavity, pharynx, larynx, squamous cell carcinoma of the esophagus, liver, breast, colorectal, and pancreas [29]. The consumption of alcoholic beverages increases the risk dose-dependently, but even light alcohol use may increase the risk for some cancers [30]. Alcohol exerts both acute and chronic effects on the cardiovascular system. The consequences in the long-term are controversial, as cardiovascular risk depends on the amount and pattern of alcohol consumption, individuals' characteristics, and the particular outcome of interest [31,32]. Some studies have reported reduced cardiovascular mortality and ischemic heart disease associated with light or moderate alcohol consumption; others show no benefit [33,34]. Moreover, all the evidence comes from observational studies, so confounding and accuracy of alcohol exposure data are also relevant issues [35]. Nevertheless, the potential and dubious benefits of alcohol in cardiovascular outcomes must be weighed against the harmful effects on other health and social consequences [36]. Thus, the safest alcohol dose remains zero [37].

Our study has some limitations. We did not know the exact date of establishment for each policy. In addition, the main effect of each policy on alcohol intake and alcohol-related health consequences could notably vary. For example, taxation and pricing policies could have a faster effect on decreasing alcohol use than other policies. The data source does not allow us to capture how a country's score has changed over time, thus we cannot establish causality, and we did not perform a spatiotemporal effect analysis. Importantly, the data on policies reflect the existence of policies, but not how they were implemented. Countries with higher incomes could have had a better implementation of PHP for longer periods while having better health indicators. Also, data from policies were collected by WHO using a questionnaire and relied on accurate reporting by the country teams. Another relevant aspect involves the impact of cultural attitudes to alcohol, which can vary notably among countries (i.e., the acceptance of social drinking or religious restrictions, among others), and it is difficult to capture in these models. Since alcohol-attributable conditions are associated with a large degree of stigma, several consequences due to alcohol misuse could be coded as non-alcoholic and, therefore, underestimated. Along with that, the use of codes could vary within countries and regions during the observed period, affecting the estimation of outcomes. Although some countries obtained a maximum score of 100 because they had better preparedness than others, they still had room for improvement in policies and implementation. Our models do not include data on specific restrictions to alcohol access in some places and regions, nor the pattern of alcohol consumption (i.e., heavy drinkers and binge drinkers). Also, some policies (such as MUP or health warning labels on alcoholic beverages) and the tax range for alcoholic beverages per country were not included in the instrument nor the models because WHO did not include them in the GISAH repository in 2010. Important variability in terms of establishment and implementation of PHP can have been observed in some countries (i.e., the United States or the United Kingdom), and other confounders, such as population density, ethnicity, medical comorbidities, and educational level were not included in our models. However, we included the HDI and HAQ index in these models to partially overcome that risk. Although ecological fallacy is one of the main risks of an ecological study, a prior study conducted in the United States, a heterogeneous country in many aspects, demonstrated an association between alcohol-related policies and lower ALD mortality [21]. Finally, our study did not evaluate data during the COVID-19 pandemic, since the pandemic may alter the interpretation of public policies, strategies, and collaborative efforts to reduce alcohol-related health consequences.

In conclusion, we developed the alcohol preparedness index to assess the establishment and strength of alcohol-related PHP worldwide. Countries with a higher preparedness were associated with lower mortality due to ALD, cancer, HCC, and cardiovascular disease, with substantial regional differences. This study adds to the body of evidence that at the population level, a more stringent policy environment will translate into declines in alcohol-related morbidity and mortality over time. Further natural experiment studies, assessing the introduction of specific policies (such as MUP) over time and the co-occurrence of changes (both in the policy environment and in population-level health), can supplement and expand our results. The development and implementation of alcohol-related policies should be prioritized by governments, scientific societies, and other stakeholders to address the long-term harmful effects of alcohol misuse.

Abbreviations used in this paper:

ACPI: Alcohol Control Policy Index

ACMP: Alcohol-associated cardiomyopathy

AH: Alcohol-associated hepatitis

ALD: Alcohol-associated liver disease

APC: Alcohol per capita consumption

APII: Alcohol Policy and Injury Index

AUD: Alcohol use disorder

DALYs: Disability-adjusted life years

GBD: Global Burden of Disease

GDP: Gross Domestic Product

GISAH: Global Information System of Alcohol and Health

HBV: Hepatitis B virus

HCC: Hepatocellular carcinoma

HCV: Hepatitis C virus

IAC: International Alcohol Control

IRR: Incidence rate ratio

MCA: Multiple Correspondence Analysis

MUP: Minimum unit pricing

OECD: Organization for Economic Cooperation and Development

PHP: Public health policies

WHO: World Health Organization

Authors' contributions: JPA, LAD, and EFL conceived and designed the study; LAD, EFL, JPA, FI, GA, JA, OC, MC, DV, AML, CAR, and MPM collected the data and contributed to data analysis and interpretation; JPA, LAD, EFL, OC, ML, CF, JVL, and RB performed the final analysis and drafted the manuscript; LAD, EFL, FI, GA, OC, JA, MHT, CF, ML, JPR, TGC, AVK, WK, MB, AL, EBT, WD, DS, VHS, PSK, JVL, AKS, RB, MA, and JPA participated in drafting the article and revising it critically for important intellectual content. LAD, EFL, and JPA directly accessed and verified the underlying data reported in the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. All the authors read and approved the final version of the manuscript.

Data Sharing: The authors confirm that the data supporting the findings of this study are available in the Supplementary Material. All datasets developed for this study are available from the corresponding author (JPA) upon a reasonable request via e-mail.

Declaration of Interest: We declare that we have no conflicts of interest.

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TABLES

Table 1. 5-item instrument to assess the strength of alcohol-related public health policies.

Item	World Health Organization Categories	Low-level (0 points)	Moderate-level (1 point)	Strong-level (2 points)
1. National policy to fight harmful consequences of alcohol	- National Plan *Written national policy* *National action plan for implementation of the written national policy*	Countries that do not have a written national policy	Countries that adopted a written national policy without an action plan for its implementation	Countries that have a national action plan for the implementation of the written national policy on alcohol
2. Control over production, pricing, and taxes	- Taxes control, pricing policies *Excise tax on beer* *Excise tax on wine* *Excise tax on spirits* - National license, production, and selling control *Governmental monopoly of selling* *Control of any licensing*	Countries that do not have taxes controls or do not control licensing	Countries with some regulations on alcohol production, licensing, or selling. There are taxes, but they are not established for all alcoholic beverages	Countries with strong regulations on alcohol production, licensing, and selling. There are taxes on all alcoholic beverages
3. Marketing of alcoholic beverages and restrictions to alcohol access	- Control over advertising and promotion *Regulations on alcohol advertising* *Regulations on alcohol product placement* *Regulations on alcohol sponsorship* *Regulations on alcohol sales promotion* *Health warning labels on alcohol advertisements* *Health warning labels on alcohol containers* - Restrictions to alcohol access *Restrictions for sales on hours* *Restrictions for sales on days* *Restrictions for sales on places* *Restrictions for sales on outlet density* *Restrictions for sales at specific events* *Restrictions for sales to intoxicated persons* *Restrictions for sales at petrol stations* - National legal minimum age for on-premise sales of alcoholic beverages	Countries without control over ads, restrictions to alcohol access, or a national legal minimum age for on-premise sales of alcoholic beverages	Countries with less than 50% of policies in control over ads and restrictions on alcohol access. There is a national legal minimum age for on-premise sales of alcoholic beverages	Countries with at least 50% of policies in control over ads and restrictions on alcohol access. There is a national legal minimum age for on-premise sales of alcoholic beverages
4. Drink-driving policies and countermeasures	- Driving-related policies National maximum legal BAC when driving a vehicle Penalties for drink driving	Countries without established restrictions on blood alcohol concentration when driving a vehicle or effective penalties for drink driving	Countries with established restrictions on blood alcohol concentration when driving a vehicle and effective penalties for drink driving	Countries that have zero tolerance to alcohol consumption when driving a vehicle and effective penalties for drink driving
5. Monitoring and surveillance	- Monitoring systems National government support for community action National monitoring system(s)	Countries that do not meet the definitions for the moderate- or strong-level	Countries with national government support for community action or national monitoring systems	Countries with national government support for community action and national monitoring systems

Table 2. Main baseline characteristics and alcohol preparedness index (API) of the included continents (n=5).

Region	Population+	Age structure (Percentage of individuals aged 15–64 years old)+	APC (liters of pure alcohol)**	Recorded APC**	Unrecorded APC**	Gross domestic product+	HDI+	HAQ index 2016*	Income level (Number of countries, %)+				API
									Low	Lower-middle	Upper-middle	High	
Africa	1,256,660,927	56 [53-59]	3.6 [1.4-6.6]	2.4 [0.9-4.5]	1.1 [0.8-2.3]	1,171 [679-2,280]	0.5 [0.5-0.6]	32.6 [29.6-41.9]	23 (46)	19 (38)	7 (14)	1 (2)	39.1 [28.5-52.9]
The Americas	1,008,578,099	66 [65-68]	6.4 [4.8-8.9]	5.5 [3.5-7.5]	1.1 [0.8-1.5]	8,821 [5,582-16,054]	0.8 [0.7-0.8]	63.6 [57.4-68.5]	0 (0)	7 (20)	19 (54.3)	9 (25.7)	50.7 [26.8-73.7]
Asia	4,344,961,323	65 [62-69]	3.3 [0.6-6.9]	2.1 [0.1-4.5]	1.0 [0.3-2.0]	4,136 [1,856-9,813]	0.7 [0.6-0.8]	61.6 [44.5-70.6]	3 (9.1)	16 (48.5)	8 (24.2)	6 (18.2)	58.8 [40.6-73.7]
Europe	838,947,256	65 [64-68]	11.1 [8.9-12.0]	9.3 [7.4-10.9]	1.4 [0.7-2.0]	23,604 [9,828-48,771]	0.9 [0.8-0.9]	88.0 [77.8-93.4]	0 (0)	1 (2.2)	13 (28.3)	32 (69.6)	77.0 [54.4-93.7]
Oceania	30,481,816	65 [61-65]	10.6 [5.5-10.7]	8.8 [4.5-9.3]	1.2 [0.5-1.8]	41,558 [1,655-55,057]	0.9 [0.6-0.9]	92.4 [26.5.4-95.9]	0 (0)	1 (33.3)	0 (0)	2 (66.7)	47.6 [26.8-87.7]
Global	7,479,629,421	65 [59-67]	6.6 [2.8-9.7]	4.7 [1.7-8.0]	1.2 [0.6-2.0]	6,109 [1,725-17,448]	0.8 [0.6-0.9]	63.6 [40.0-78.1]	26 (15.6)	44 (26.4)	47 (28.1)	50 (29.9)	54 [34.9-76.8]

Abbreviations: *APC: alcohol per capita consumption, HDI: human development index; HAQ: healthcare access and quality.*

**Updated to 2016*

***Updated to 2018*

+Updated to 2019

Data into brackets is the interquartile range.

Table 3. Dimensions of the alcohol preparedness index (API) and the degree of establishment among the 169 countries of the five continents studied.

Continent	Establishment of each dimension (N, %)														
	1. National policy to fight harmful consequences of alcohol			2. Control over production, pricing, and taxes			3. Marketing of alcoholic beverages and restrictions to alcohol access			4. Drink-driving policies and countermeasures			5. Monitoring and surveillance		
	Low	Moderate	Strong	Low	Moderate	Strong	Low	Moderate	Strong	Low	Moderate	Strong	Low	Moderate	Strong
Africa (N=50)	39 (78)	6 (12)	5 (10)	4 (8)	26 (52)	20 (40)	27 (54)	13 (26)	10 (10)	13 (26)	31 (62)	6 (12)	25 (50)	22 (44)	3 (6)
The Americas (N=35)	25 (71.4)	3 (8.6)	7 (20)	8 (22.9)	22 (62.9)	5 (14.2)	17 (48.6)	110 (28.7)	8 (22.9)	9 (25.7)	25 (71.4)	1 (2.9)	4 (11.4)	17 (48.6)	14 (40)
Asia (N=33)	17 (51.5)	5 (15.2)	11 (33.3)	4 (12.1)	18 (54.6)	11 (33.3)	10 (30.3)	10 (30.3)	13 (39.4)	1 (3.0)	22 (66.7)	10 (30.3)	10 (30.3)	15 (45.5)	8 (24.2)
Europe (N=46)	16 (34.8)	14 (30.4)	16 (34.8)	6 (13)	34 (74)	6 (13)	9 (19.6)	24 (52.2)	13 (28.2)	0 (0)	40 (87)	6 (13)	8 (17.4)	9 (19.6)	29 (63)
Oceania (N=5)	3 (60)	1 (20)	1 (20)	3 (60)	1 (20)	1 (20)	2 (40)	2 (40)	1 (20)	1 (20)	4 (80)	0 (0)	1 (20)	2 (40)	2 (40)
Total (N=169)	100 (59.2)	29 (17.2)	40 (23.6)	25 (14.8)	101 (59.8)	43 (25.4)	65 (38.5)	59 (34.9)	45 (26.6)	24 (14.2)	122 (72.2)	23 (13.6)	48 (28.4)	65 (38.5)	56 (33.1)

FIGURE LEGENDS

Figure 1. Heatmap of the Alcohol Preparedness Index (API) obtained for each country in 2010. The preparedness index ranges from 0 to 100, being 0 the lowest preparedness and 100 the highest.

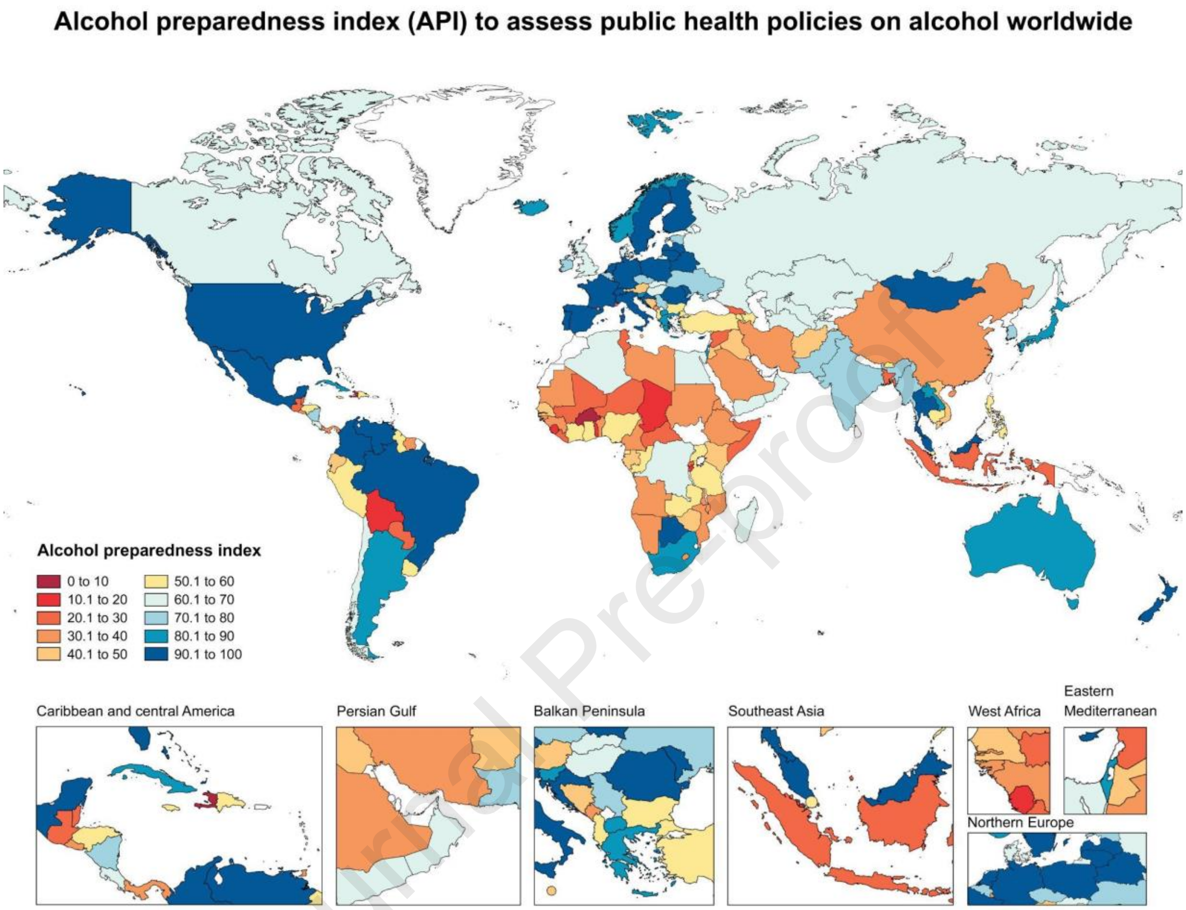
Figure 2. Relationship between the Alcohol Preparedness Index (API) and the burden of disease due to alcohol. (A) alcohol use disorder (AUD) prevalence, (B) deaths due to cirrhosis, (C) alcohol-associated liver disease (ALD) mortality, (D) deaths due to cancer, (E) incidence of alcohol-attributable Hepatocellular carcinoma (HCC), (F) deaths due to alcohol-attributable HCC, (G) cardiovascular mortality, and (H) alcohol-associated cardiomyopathy prevalence. The preparedness index ranges from 0 to 100, being 0 the lowest preparedness and 100 the highest.

Figure 3. Association between alcohol-related public health policies and alcohol use disorder (AUD) prevalence over time. The main predictor corresponds to an interaction between time in years and the Alcohol Preparedness Index (API). The model was adjusted by population size, age structure, healthcare access and quality (HAQ) index, and the interaction of the human development index (HDI), GINI index, and gross domestic product (GDP) over time.

Figure 4. Association between alcohol-related public health policies and alcohol-associated liver disease (ALD) mortality over time. The main predictor corresponds to an interaction between time in years and the Alcohol Preparedness Index (API). The model was adjusted by population size, age structure, healthcare access and quality (HAQ) index, and the interaction of the human development index

(HDI), GINI index, and gross domestic product (GDP) over time.

FIGURES



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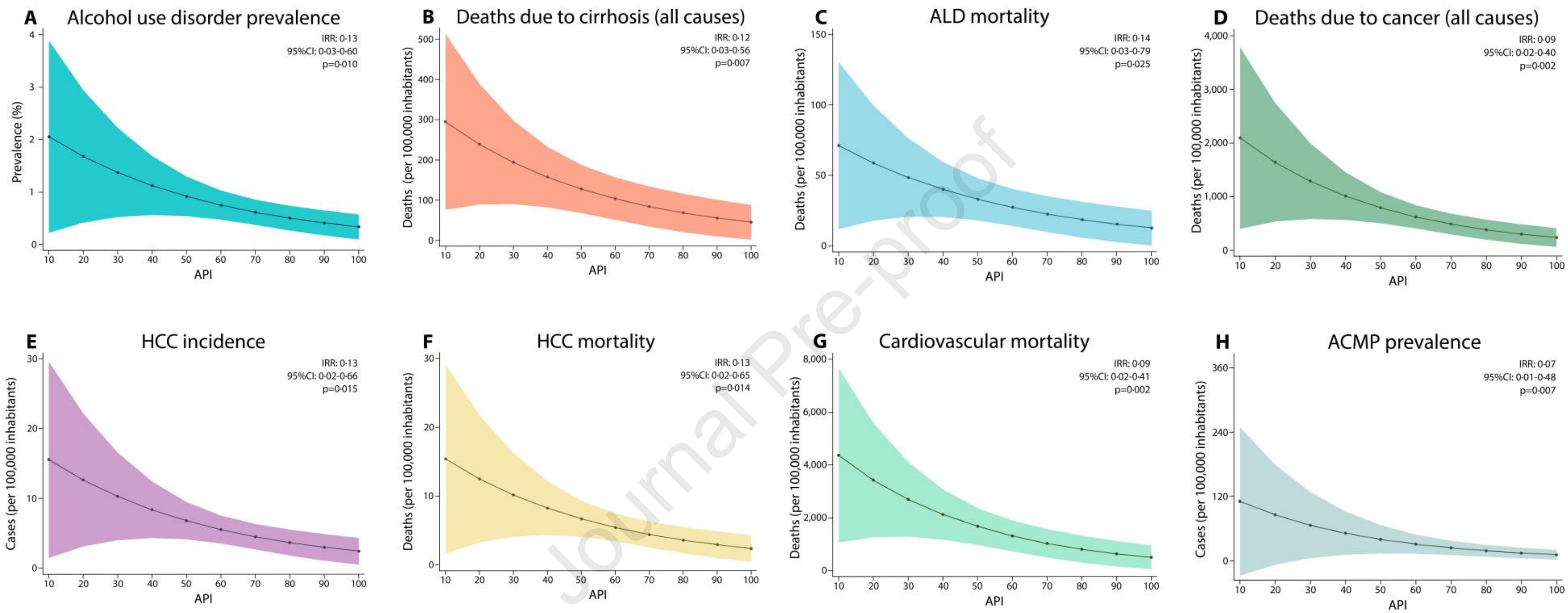

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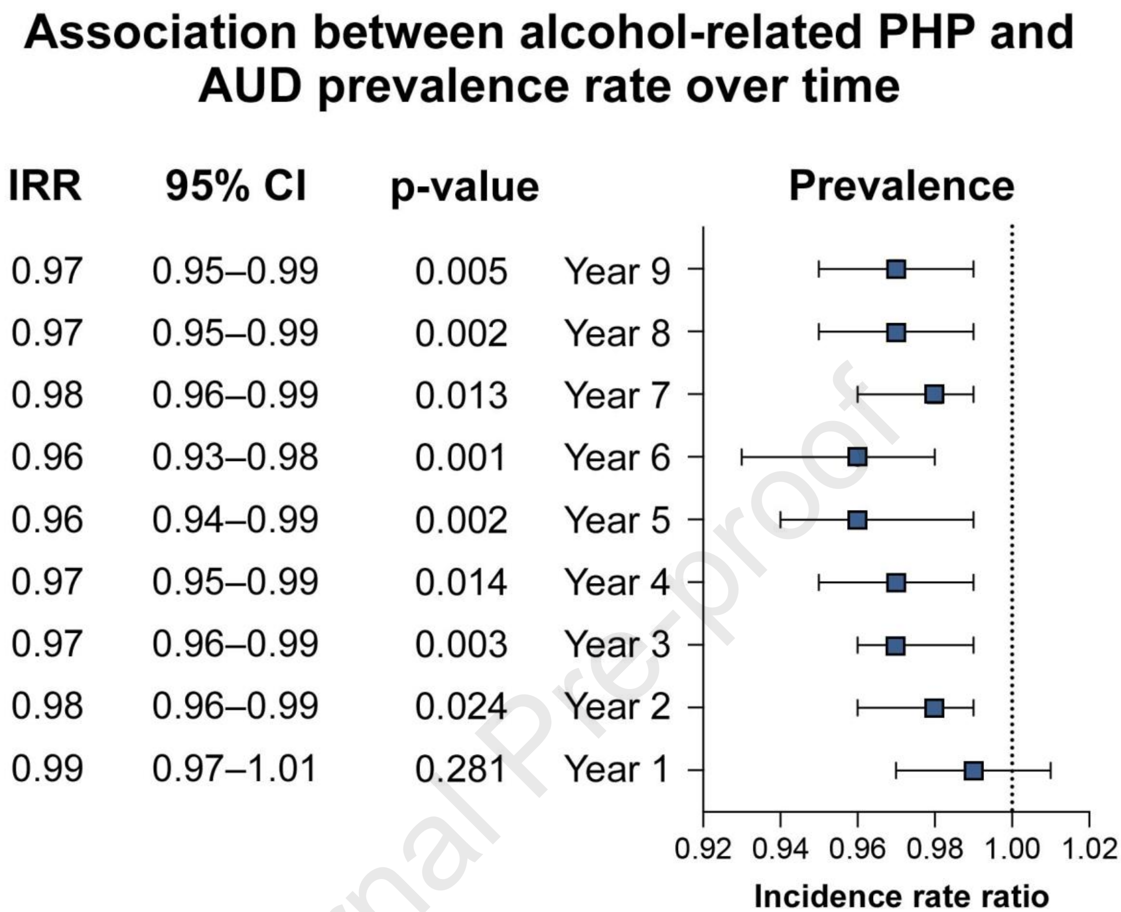

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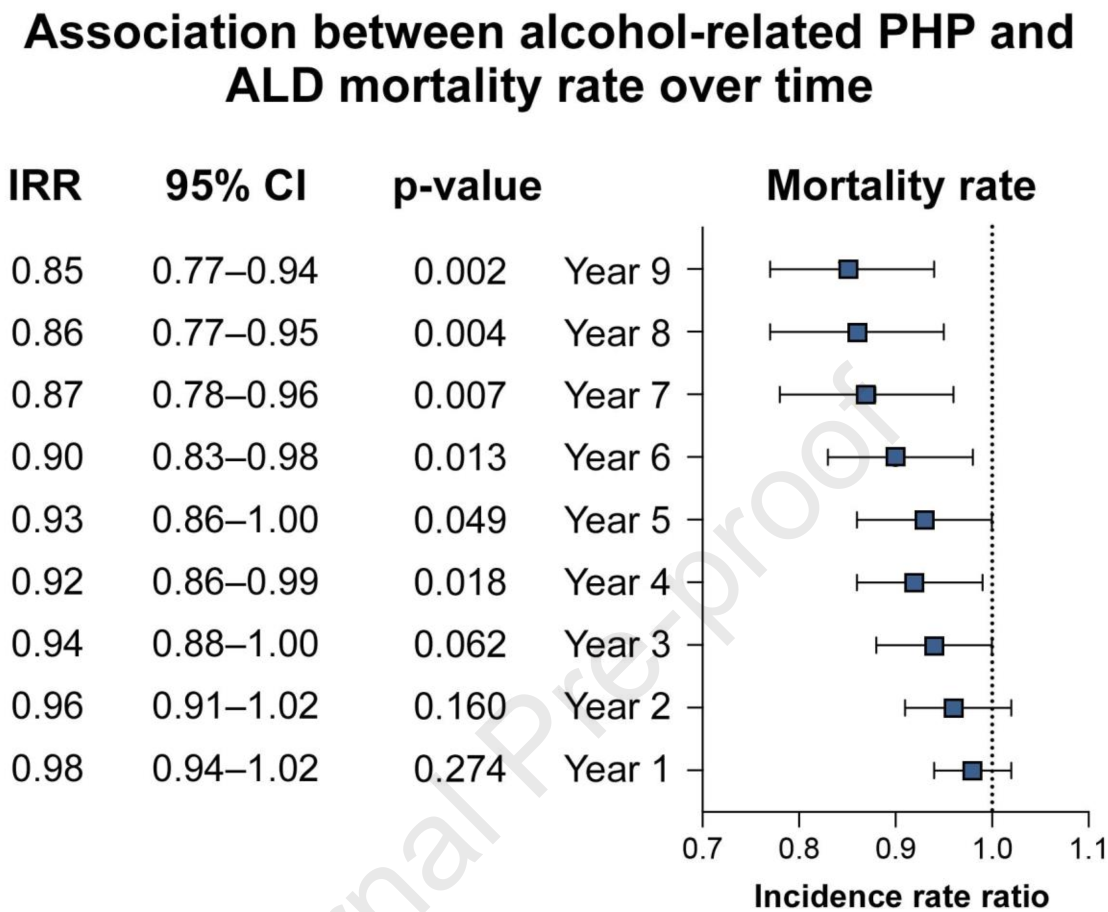

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HIGHLIGHTS

- The *Alcohol Preparedness Index* (API) is a new instrument to assess the existence of alcohol-related public policies for each country.

- A more stringent policy environment correlates with declines in alcohol use disorder prevalence and alcohol-associated liver disease mortality over time.

- The strengthening of alcohol-related public health policies could also impact long-term mortality rates from cardiovascular disease, alcohol-attributable hepatocellular carcinoma, and other neoplasms.

- The association between API and alcohol-related outcomes became more robust over time, which indicates that the benefits of a stricter policy environment become more evident over time.