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How Much is Too Much? A Methodological Investigation of the Literature on Alcohol Consumption

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A methodological investigation of the literature on alcohol consumption

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Abstract

Until a few years ago, moderate alcohol consumption was thought to have (mild) beneficial effects on health. However, some recent studies have suggested that "there is no safe level" of alcohol intake. Consequently, public health institutions have responded by advising against any level of alcohol use and suggesting governments a number of policies to reduce the overall alcohol consumption. Nonetheless, medical studies suffer from a variety of methodological issues that could undermine the reliability of the findings, especially when focusing on low-intake levels. We apply a search algorithm to extract 19,981 Confidence Intervals (CIs) from 6,763 medical abstracts, and show the existence of a clear publication bias which appears to have even increased and not decreased, in recent years. Further, we assess the quality of a sample of articles, showing the presence of several limitations such as omitted variable bias, miscalculation of alcohol intake, use of linear in place of non-linear models, and lack of validation of Mendelian Randomization (MR) assumptions. We conclude that the methodological limitations of the literature preclude us from claiming that "there is no safe level" of alcohol intake.

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1 Introduction

Alcohol abuse is one of the leading causes of death, especially among males and younger consumers. According to the World Health Organization, more than 200 health conditions are connected to harmful alcohol use, including liver and cardiovascular diseases, road injuries and violence, cancers, suicides, tuberculosis, and sexually transmitted diseases (WHO, 2019). The Centers for Disease Control and Prevention (CDC)[1] calculate that more than 140,000 people die from excessive alcohol use in the U.S. each year. Worldwide, a similar count by the WHO (2019) amounts to 3 million deaths, more than tuberculosis and HIV/AIDS. The picture becomes even more worrisome if we expand the analysis to the negative consequences on chronic diseases, fetal alcohol spectrum disorders, mental health and other issues of interest for policy makers. According to the CDC, if we consider the sole healthcare, workplace productivity, collisions and criminal justice, the costs of excessive alcohol use represent a 249 billion $/year loss for the U.S. economy, while the OECD (2021) estimates that in OECD countries the GDP is 1.6% lower due to diseases caused by alcohol consumption above the 1-1.5 drinks per day cap.

While excessive alcohol consumption has indisputable negative consequences, the effect of moderate alcohol consumption is less clear. For a long time, a consistent body of literature has shown the positive or null effect of moderate consumption. In most observational studies the association between alcohol use and health was U- or J-shaped, and moderate alcohol use (1-2 drinks per day) was found to have a mild negative or possibly null association with cardiovascular diseases (see Ronksley et al. 2011, Reynolds et al. 2003) and diabetes (Carlsson et al., 2005). This belief was so rooted in the academic community that, in the Dietary Guidelines for Americans 2010 provided by the U.S. Government, the health advice was that moderate alcohol use is protective against the aforementioned diseases and reduces all-cause mortality.[2]

However, in the last decade, this consensus has gradually weakened. A series of scientific studies, such as Griswold et al. (2018), started to claim that there is no safe level of alcohol intake. Subsequently, prestigious newspaper - e.g. the New York Times in 2018 and 2023 [3] - quickly republished this information, adopting this new point of view. The same dynamic has also pervaded the institutions responsible for public health and policy. For instance, the Dietary Guidelines for Americans 2015 do not claim beneficial effects of moderate con-

[1] See `https://www.cdc.gov/alcohol/features/excessive-alcohol-deaths.html` accessed on December 30, 2022.

[2] "Alcohol consumption may have beneficial effects when consumed in moderation. Strong evidence from observational studies has shown that moderate alcohol consumption is associated with a lower risk of cardiovascular disease. Moderate alcohol consumption also is associated with reduced risk of all-cause mortality among middle-aged and older adults and may help to keep cognitive function intact with age" (DGAC (2010), p. 49).

[3] See `https://www.nytimes.com/2023/01/13/well/mind/alcohol-health-effects.html` and `https://www.nytimes.com/2018/08/27/health/alcohol-drinking-health.html`

sumption anymore and do not recommend that people start drinking for any reason.[4] Further, in September 2022 the WHO Regional Office for Europe approved the "European framework for action on alcohol 2022-2025"[5]. According to this document, the WHO suggests reducing per capita alcohol consumption by 2025 (from a 2010 baseline) by ten percent. Concretely, they suggest that European governments undertake actions such as increasing taxes, implementing minimum pricing policies, increasing minimum age restrictions, introducing total bans in and around sporting and cultural events, limiting content and frequency of commercial communications, and so forth. In June 2022, the Irish Government informed the European Commission (EC) of its intention to introduce health warnings about the risks of cancer and liver diseases linked to alcohol intake [6]. Despite protests from Italy, Spain and six other EU member states, the request did not receive any objection from the European Commission during a six-month moratorium period [7].

The WHO strategy appears to be well defined; according to it, there is no safe level of alcohol intake, and there is no distinction among typologies of alcoholic beverages. For instance, spirits and wines should be subjected to the same restrictions, irrespective of the average consumption and the modalities (e.g., mostly during lunch, or binge drinking). This approach seems to be at odds with the previous WHO's strategy (WHO, 2010), which mainly focused on reducing the *harmful* level of consumption. The proposal is also distant from the Cancer Plan approved by the European Parliament in February 2022 (EC, 2022), that focused on tackling *excessive* – rather than average – consumption. This shows that even among institutions there is no consensus on the effects of moderate alcohol intake. Assuming that European countries implemented the policies proposed by the WHO, a 10% reduction in alcohol consumption would cause company bankruptcies, job losses and damage to tourism. The alcoholic beverage industry includes producers, distributors, sellers, hospitality providers such as hotels, and has a relevant role in the economy. In Southern Europe, some regions have created specific food and wine tours. The value of the global alcoholic industry was estimated to be more than 500 billion $ in 2020, without including hospitality[8]. The Institute for Alcohol Studies (IAS, 2020) estimates that in the UK, including hospitality services, the alcoholic beverage industry was worth 46 billion £ in 2014, accounting for 2.5% of GDP and 770,000 jobs.

[4] "The Dietary Guidelines does not recommend that individuals who do not drink alcohol start drinking for any reason" (DGAC (2015), p. 59). "If adults aged 21 years and older choose to drink alcoholic beverages, drinking less is better for health than drinking more" (DGAC (2020), p. 49).

[5] See `https://www.who.int/europe/publications/i/item/EUR-RC72-BG-4`

[6] See `https://www.europarl.europa.eu/doceo/document/$E-9-2022-003729_EN.html$`

[7] See `https://www.theguardian.com/world/2023/jan/12/italy-ireland-plans-for-alcohol-health-warnings-wine`; accessed on January 16, 2023

[8] See https://www.businesswire.com/news/home/20210817005734/en/Alcoholic-Beverages-Global-Market-Report-2021-COVID-19-Impacts-and-Forecaststo-2030—ResearchAndMarkets.com; accessed on December 30, 2022.

In front of clear scientific evidence on serious health issues arising from moderate alcohol consumption, the economic consequences could eventually take second place. However, it appears that there is no scientific consensus on this topic. The crucial - and arguable - point raised by WHO Europe is that "to identify a 'safe' level of alcohol consumption, valid scientific evidence would need to demonstrate that at and below a certain level, there is no risk of illness or injury associated with alcohol consumption"[9]. However, it is not at all clear with whom the burden of proof lies and the reverse can be claimed, that is, in order to identify an 'unsafe' level of alcohol consumption, valid scientific evidence would need to demonstrate that at and below a certain level, there is a risk of illness or injury associated with alcohol consumption. The main issue is that, when studying the effects of alcohol (as well as those of food and drugs), it is not possible to conduct long-term Randomized Controlled Trials (RCT) because of both ethical and practical reasons (Au Yeung et al., 2013a; Poli et al., 2013). Indeed, the literature on the long-term effects of alcohol on health relies on observational studies where articles show at least one of the following statistical and methodological flaws: publication bias, omitted variable bias, reverse causality, inclusion of former drinkers in the teetotalers' group ('sick-quitter hypothesis'), poor recall of past alcohol consumption, underestimation of the real alcohol intake, non-distinction for ethnicity, inappropriate use of linear models in place of non-linear models.

Nowadays, one of the most used methods to remedy some of these problems is the Mendelian Randomization (MR). This methodology is similar to an instrumental variables approach and allows to establish the causal role of moderate alcohol consumption in a suitable population where a genetic variant affects alcohol metabolism and thereby alcohol use (van de Luitgaarden et al. 2022). While MR appears very promising, it requires more assumptions than RCT and is likely to suffer from significant biases (e.g., VanderWeele et al. 2014; Nitsch et al. 2006; Adam 2019). In fact, three assumptions must be fulfilled for the validity of MR: (1) the genetic variant must be associated with the exposure of interest; (2) the genetic variant should not associate with confounder; and (3) the genetic variant only affects the outcome through the exposure to alcohol. There are many situations in which these assumptions might be violated. One such situation is genetic pleiotropy, i.e., a scenario in which a genetic variant affects both the drinking habits and the smoking behavior. As pointed out in Nitsch et al. (2006), MR cannot replace RCT, and presents various potential sources of bias such as inadequate phenotype definition, the presence of gene-environment or gene-gene interactions, the possibility of reverse causation, and linkage disequilibrium.

In this study, we explore all the aforementioned sources of bias and examine the policy implications of our findings. First, we address the issue of publica-

[9]see `https://www.who.int/europe/news/item/04-01-2023-no-level-of-alcohol-consumption-is-safe-for-our-health` accessed on 16th of May 2023

tion bias by extracting CIs from all alcohol-related papers published in the last decades and available on Pubmed. Second, we conduct a rigorous methodological analysis of a sample of papers from WHO's 2018 report, the CDC website, and studies that use the MR approach. Finally, we discuss the reasons behind the zero alcohol campaign by newspapers and institutions, despite the methodological flaws of the scientific papers regarding moderate consumption.

2 Publication Bias

It is a well known fact that it is easier to publish works in the presence of statistically significant results (see Emerson et al., 2010). This encourages researchers to only submit manuscripts that present significant findings and, in some cases, even to manipulate their results to obtain a p-value less than 0.05. Ultimately, this causes a drastic increase in false positive results (see Dumas-Mallet et al., 2017). Allen and Mehler (2019) find that the most effective way to prevent this problem is to adopt study preregistration and registered reports (RRs) where the hypotheses and analysis pipelines are declared publicly before collecting the data. The authors survey 113 published biomedical and psychological science RRs compiled by the Center for Open Science and find that 60.5% do not get statistically significant results, compared to a share between 5% and 20% for the traditional literature. There are several strategies researchers can rely on to force the results. One way is to include or exclude some observations, which is particularly common in medical science due to the exclusion restrictions of patients from trials based on age, co-morbidity and co-prescribing. In their systematic review, He et al. (2020) find that the estimated rates of exclusion from trials varied from 0% to 100%, and the median exclusion rate was 77.1% of patients. Another way to influence the results is to choose a statistical model which achieves the target. In their experiment, Silberzahn et al. (2018) ask 29 teams involving 61 analysts to address the same research question using the same identical dataset. The question is whether soccer referees are more likely to give red cards to dark-skin-toned players than to light-skin-toned players. Both the statistical methodologies and the results vary widely across the teams of researchers, with the estimated effect sizes ranging from 0.89 to 2.93 in odds-ratio units; 20 teams find a statistically significant positive effect while 9 do not any.

The problem of publication bias is so common that in many disciplines academics have created new journals devoted specifically to publish articles with non-significant results in order to provide an unbiased vision of the reality. In Psychology there is the *Journal of Articles in Support of the Null Hypothesis*; in Medicine the *Journal of Negative Results in Biomedicine* (where negative should be interpreted as non-significant); in Ecology and Evolutionary Biology there is the *Journal of Negative Results* (same as before); in Economics there is the *Series of Unsurprising Results in Economics* (SURE). In order to investigate this issue, we adopt the same strategy used by Barnett and Wren (2019) and van Zwet and Cator (2021). By using a modified version of the algorithm created by Georgescu and Wren (2018), we extract confidence intervals from the abstracts of all the published papers uploaded on PubMed from 1980 to 2022 containing the word "alcohol" in the title or the expression "moderate alcohol" in the abstract. Pubmed Central (PMC) carefully controls whether journals meet certain scientific quality standards. We exclude those journals which are considered potentially predatory in the updated Beall's list provided by Open Access Journals [10]. After selecting only the papers containing at least one CI in the abstract, we obtain a data set consisting of 6,763 papers and a total of 19,981 CIs. Subsequently, we convert the CIs to z-values.

As shown in Figure 1, our results display a suspiciously low number of z-values between -1.96 and +1.96, which suggests the presence of publication bias. To investigate time trends, we compute for each year the ratio between the number of CIs just above the significance level threshold (1.96 < |z-value| < 2.58, which corresponds to a p-value between 0.01 and 0.05) and the number of CIs just below (1.64 < |z-value| < 1.96, which corresponds to a p-value between 0.05 and 0.10). Figure 2 shows how the ratio increases over time, suggesting that publication bias is becoming even more common. As a last step of this analysis, we investigate the relationship between the SCImago Journal Rank (SJR) and the presence of insignificant results ($p > 0.05$) for a sub-sample of 3.217 papers for which the SJR was readily available. The mean and median of the SJR are slightly - yet significantly - higher in the group of papers displaying at least one insignificant result in the abstract (mean: 2.10 vs 1.97; median: 1.76 vs 1.54, respectively; see Figure 3). This suggests that higher impact journals are more likely to publish results that do not achieve statistical significance, thus reducing the severity of the publication bias.

3 Assessment of methodological research quality

In this section, we present our examination of 49 published articles on the effects of alcohol consumption on health. Our goal is to investigate the possible presence of methodological flaws or important limitations that may hinder the interpretation of the results.

We consider original empirical studies that attempt to establish the effects of alcohol consumption on specific diseases, overall mortality and risky behaviors such as unprotected sex. We select the studies from three distinct sources. The first is the most recent Global Status Report on Alcohol Consumption and health (WHO, 2019) that cites 397 papers. We exclude 161 meta-analyses, literature reviews, reports or newspaper articles, and 214 articles that are not relevant to our analysis, such as papers evaluating the impact of policies contrasting alcohol abuse or studies on the determinants of alcohol consumption. From the

[10]See: `https://www.openacessjournal.com/blog/predatory-publishers/`

report, we identify 22 papers to be included in our analysis. The second source is the CDC website, specifically the Alcohol & Public Health section[11]. At the day of access, the web page presented 109 publications, but just five of them meet our inclusion criteria, while 40 are reports or literature reviews and 64 are papers on different subjects. The third source is the work by van de Luitgaarden et al. (2022), that presents a meta-literature review on articles using the Mendelian approach to assess the effects of alcohol. After excluding a meta-analysis, 23 out of the 24 papers are used in our research. We identify only one case of overlap between two of the three sources; therefore, the final number of observations is 49. A complete list of the selected studies is presented in Table 1.

We assess the presence of potential sources of bias, including omitted variable bias, estimation method, assessment of alcohol consumption, and the validity of studies based on Mendelian randomization. In total, we define 16 binary indicators (+3 that only apply to papers that use MR), such that a value of 1 indicates a "good" trait (i.e., the corresponding source of bias is either absent, or handled correctly), while a value of 0 indicates a "bad" trait (i.e., the paper is likely to suffer from some bias). Occasionally we assign a score of 0.5, whenever the authors handled the issue partially. A missing value is assigned when the bias is not relevant, such as an assessment of diet in a work studying the effect of alcohol intake on car accidents. A complete list of our binary indicators is available in Table 2. To determine to which extent the authors have taken into account the potential sources of bias, we also calculate a "quality score" for each paper, defined as the mean of all the binary indicators.

In Figure 4, we present the distribution of the quality score for the selected 49 papers, from highest to lowest. The mean value of the score is around 0.5, indicating that, on average, papers control for half of the potential sources of bias. Figure 5 displays the percentage of papers that appropriately analyze each specific source of bias. All of the MR papers validate the second assumptions, and nearly all the papers in our sample include controls for sex and age. However, only one paper examines the differential impacts of specific alcoholic beverages, such as wine and spirits. Additionally, other relevant aspects such as life-time alcohol consumption patterns or use of drugs are considered by a minority of the papers. We test the existence of a relationship between the year of publication of the selected papers and their quality score, but no trend is observed. Finally, we examine the association between the Scimago Journal Ranking, measured both in the year of publication and in 2021, and our quality score. Our findings suggest that journals with higher SJR values in the year of publication have a slightly better quality. However, the difference disappears when we consider the normalized SJR values for 2021 (see Figure 6).

In summary, our analysis shows that papers included in our study suffer from various sources of bias that may undermine the validity of their estimations of the effects of alcohol. Some might argue that health policies are based on more

[11]see: `https://www.cdc.gov/alcohol/publications.htm`, accessed on March 15, 2023

comprehensive studies, such as meta-analyses, which combine the results from multiple individual studies. Indeed, a substantial number of papers cited by the WHO report and the CDC website are meta-analyses. This type of study is particularly appreciated by health institutions, as they allow to use a large number of observations and improve the statistical inference (e.g., Griswold et al., 2018). Nonetheless, as underlined by some scholars[12], increasing the sample size does not eliminate the bias. The mean of multiple biased estimators is still biased, unless the individual biases have zero mean and "cancel out". The problem is even more severe in the presence of the aforementioned publication bias which reduces the chances that studies finding non-significant relationships get published.

4 Discussion and conclusion

The evidence provided in the previous sections shows that the literature on (moderate) alcohol consumption and health presents various statistical and methodological flaws. Because of moral and practical reasons, it is not possible to carry on Randomized Controlled Trials (RCTs) where the treatment sample is forced to drink a certain amount of alcohol every day for many years while the control one is forbidden to. Therefore, we have to rely on studies based on observational data which suffer from many weaknesses such as reverse causality, omitted variable bias, specific potential sources of bias related to alcohol consumption, estimation method issues, and the validation of the three Mendelian assumptions. It is objectively impossible to control for all the relevant variables, therefore all studies are expected to be more or less biased.

Despite all the above limitations, the negative effect of alcohol abuse is so strong that cannot be denied. What is unclear is whether *moderate* alcohol consumption is harmful and, in case, what is the safe limit we should not exceed. Excessive consumption of alcohol, marijuana, cigarettes, red meat, cheese, butter, eggs, coffee etc. are surely unhealthy. However, it is difficult – if not impossible – to say whether one glass of wine per day, one cigarette per week, or one beef steak per month have negative and detectable effects on health, net of other omitted confounding elements. Thus, we are unable to determine exactly how much is too much. Nevertheless, a growing number of academic studies and newspaper articles suggests that even a “little alcohol can harm you” or that “there is no safe level”. Why is that?

One reason could be that, in terms of strategic health communication, a unique and simple message is more effective than many distinctions. The Health Communication Unit of the University of Toronto 2012 firmly claims that every medical message should be clear while the Health Communication Playbook of the U.S. Department of Health and Human Services 2018 states that every communication strategy should start with the identification of (no more than

[12] https://www.parentdata.org/p/alcohol-and-health

three) key messages which should be short and concise, memorable, focused on a specific topic, and consistent. The literature has shown that alcohol tolerance is higher when consumers are males, adults, and heavier; when they drink during meals and distribute the same amount of alcohol over the week, instead of concentrating it in a short period of time (binge drinking); when they have good health and do not take medicines; when they do not have genetic anomalies which prevent alcohol from being processed properly (see Castriota, 2020 ch. 2 and 7 for a review). Since the individual tolerance depends on many factors and it is impossible to determine precisely the limit of each person, consumers could develop the misleading belief that the unsafe limit is "being drunk", which would incentivize excessive drinking. In line with the aforementioned suggestions, simple messages saying that "there is no safe level" and that "people who have never drunk should not start drinking for any reason" overcome this problem. However, as suggested by The Health Communication Unit of the University of Toronto 2012, we should also ask the audience to take reasonably easy actions. When it takes too much effort and sacrifice, a behavior can become unacceptable; this is the reason why abstinence has not been a very effective strategy for alcohol, tobacco and drugs. The same Unit suggests more modest but feasible targets and policies to achieve. In 2018, the NIAAA stated that reducing the WHO risk drinking level outcomes is the preferred goal of most patients and is more readily achieved as a measure of success than "abstinence" or "no heavy drinking days"[13]. Furthermore, its study shows that heavy drinkers who subsequently reduce their risk drinking level report long-lasting clinically significant improvements in how they feel and function. Important sacrifices such as complete abstinence can become even more unacceptable if the scientific evidence is not very solid and there is no consensus among researchers. In their experimental analysis Chinn et al. (2018) show that communicating higher levels of consensus increases perceptions of scientific certainty, which is associated with greater personal agreement and policy support. Therefore, the combination of these costly sacrifices and lack of consensus could generate counterproductive effects among consumers and undermine trust in medical science.

Another reason for the zero-alcohol campaign could be the polarization which sometimes takes place in medical research. The 2010 Dietary Guidelines for Americans suggest to "reduce daily sodium intake to less than 2,300 milligrams (mg) and further reduce intake to 1,500 mg among persons who are 51 years of age and older and those of any age who are African American or have hypertension, diabetes, or chronic kidney disease". However, in its assessment of evidence on the effect of sodium intake on populations, the Institute of Medicine (2013) concludes that – despite methodological flaws and limitations similar to the ones identified in our work – the scientific evidence indicates a positive association between sodium intake and risk of cardiovascular diseases (CVD). Nevertheless, the same same literature is inconsistent and insufficient to conclude that lowering sodium intakes below 2,300 mg has any additional health

[13]see `https://www.fda.gov/media/131766/download` accessed on May 15, 2023

benefits. Trinquart et al. (2016) claim that several public health organizations have recommended population-wide reduction in salt intake, even though the benefits are unclear. The authors analyze 269 reports addressing the effect of sodium intake on cerebrocardiovascular disease or mortality and find that 54% were supportive of the hypothesis that salt reduction leads to health benefits, 33% were contradictory, and 13% were inconclusive. Even more interestingly, reports were 1.51 times more likely to cite works that drew a similar conclusion, than to cite works drawing a different one. With respect to salt, alcohol is an even more divisive subject given the mild social and psychological benefits of moderate consumption and the strong negative health and social consequences of abuse. The polarization of the debate is deeply rooted in history: Temperance movements were born in the 18th Century and rose in the 19th due to the widespread alcoholism and the strong support by the women victims of domestic violence (see Colman, 2008; Masson, 1997). After the introduction of prohibition in 1920, with the Volstead Act, these movements have not disappeared and still influence the society and the scientific debate.

A similar polarization took place in the political debate with respect to marijuana (see Denham, 2019) and psychedelic drugs (Pollan, 2018). Throughout the 1930s, newspaper articles dramatized the dangers of marijuana (Earleywine, 2002) and in 1937 the U.S. Congress passed the Marijuana Tax Act which made possession or transfer of marijuana illegal. In the following years, despite the growing evidence that marijuana was not a serious threat – see for example the Laguardia Committee Report New York (1944) – the anti-marijuana campaign expanded and culminated with the Controlled Substances Act of 1970 which introduced a total ban of the use of cannabis and other drugs for any purpose, including medical. Only in the last decades, marijuana has been legalized in 38 States for medical use and in 21 for recreational one. Psychedelic drugs share a similar path, with the Controlled Substances Act of 1970 forbidding any use and hampering research, which however has recently grown and is showing their potential for treatment of Post Traumatic Stress Disorder - PTSD (Vollenweider and Preller, 2020). These two examples illustrate how political involvement can delay the advancement of scientific research, causing emotional divisiveness in debates that should be addressed in a purely objective way. While this behavior is highly condemnable, since politicians should prioritize the wellness of the society rather than simple electoral calculus, it is more understandable to find polarization in the political rather than in the scientific debate.

A third reason why the media and the institutions push towards a zero-alcohol target could be the misinterpretation of the direction of the bias. Alcohol consumption in population surveys is underestimated by 40% up to 65% due to underreporting by respondents and to omission of heavier drinkers from the sample resulting in non-response bias (Stockwell et al., 2014). Therefore, econometric models overestimate the negative effects of alcohol on health and the “safe limit” is actually higher than the one estimated through these downward biased data (Stockwell et al., 2018; Vance et al., 2020). If, for example, unhealthy people declared to drink two glasses per day while their actual intake was four, the negative link between alcohol and health would be overestimated and four, not two, drinks would eventually be responsible for the worsened conditions. Klatsky et al. (2014) find that the risk of any cancer is statistically not different between low (< 1 unit per day) and light-moderate drinkers (1-2 drinks per day); however, when stratifying subjects into suspected of underreporting, not suspected of underreporting, and unsure underreporting status, they find that the first group has a statistically significant higher hazard ratio than the others. Therefore, the effect of low alcohol on health found in the literature appears to be driven and biased by people who underreport their true consumption level. Others instead – like the British national agency Alcohol Concern (2009)[14] – claim that the total alcohol burden is underestimated because the actual drinking is underreported[15]. However, applying the true (higher) alcohol consumption to the overestimated negative alcohol effects would produce upward biased estimates of the total health burden.

In conclusion, given the methodological limitations in detecting the effects of modest alcohol quantities, from a scientific point of view it is incorrect to claim that "there is no safe level". We should rather say that "we are unable to determine if there is a safe amount" and, likely, we will never be.

[14] see: https://www.ias.org.uk/uploads/pdf/News%20stories/ac-report-181209.pdf

[15] "Routine survey measures of alcohol consumption in the UK grossly underestimate actual consumption. Current survey designs to measure alcohol consumption are likely to lead to underestimates in the size of the population being affected by alcohol-related harms. Consequently, this has risks for the urgency of the government's current policy response and the necessary public investment needed to reduce harms" (Alcohol Concern, 2009, p. 2).

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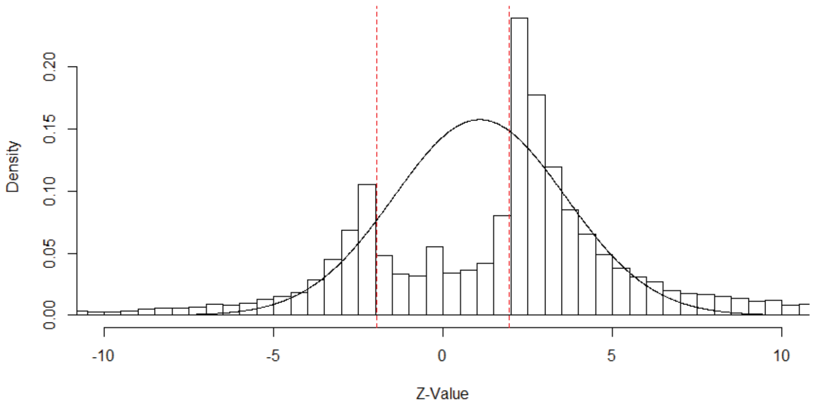
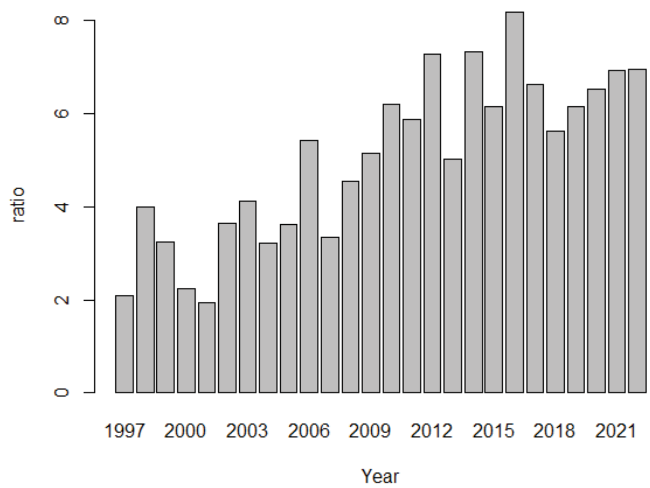
Figures

Figure 1: Distribution of z-values on alcohol-related paper from PubMed



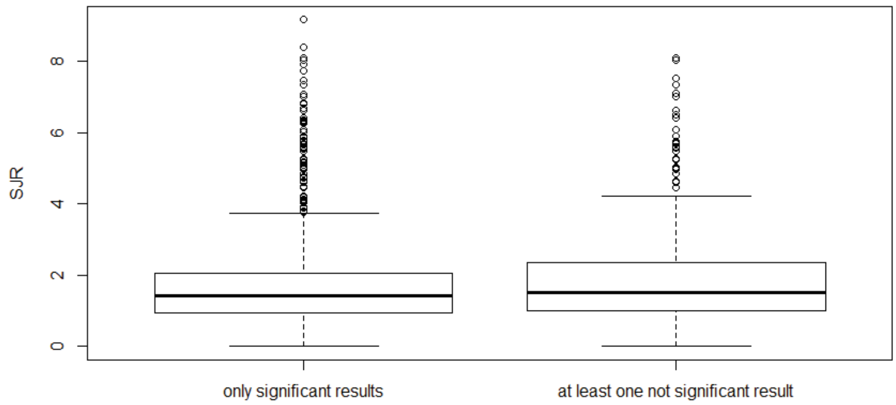
Note: in the figure, the two dashed lines represent the ±1.96 points. For this analysis, we selected from PuBMed the papers containing the word "alcohol" in the title or the expression "moderate alcohol" in the abstract, which simultaneously displayed at least one CI in the abstract. The period of analysis is from 1980 to 2022 and the final data-set consists of 6,763 papers and a total of 19,981 CIs.

Figure 2: Time trend in Publication Bias



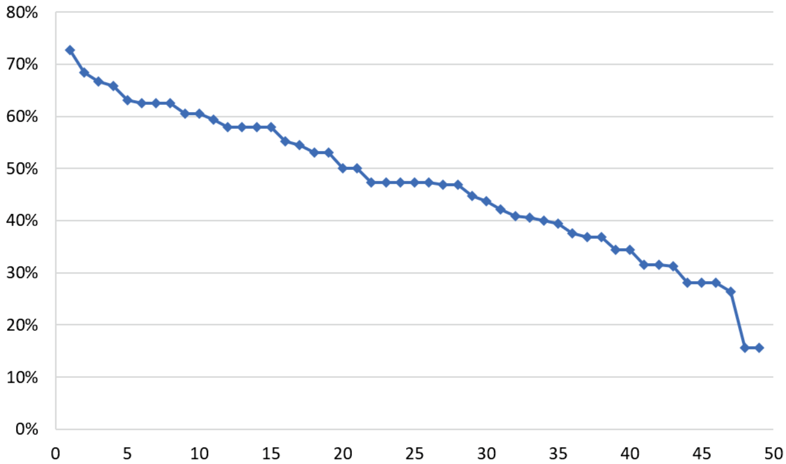
Note: Ratio between the number of CI just above the 0.05 significance level threshold ($1.96 < |\text{z-value}| < 2.58$, which corresponds to a p-value between 0.01 and 0.05) and the CI just below ($1.64 < |\text{z-value}| < 1.96$, which corresponds to a p-value between 0.05 and 0.10). We display the results starting from 1997, the first year in our sample in which the CI observations exceed one hundred.

Figure 3: The SJR and Publication Bias



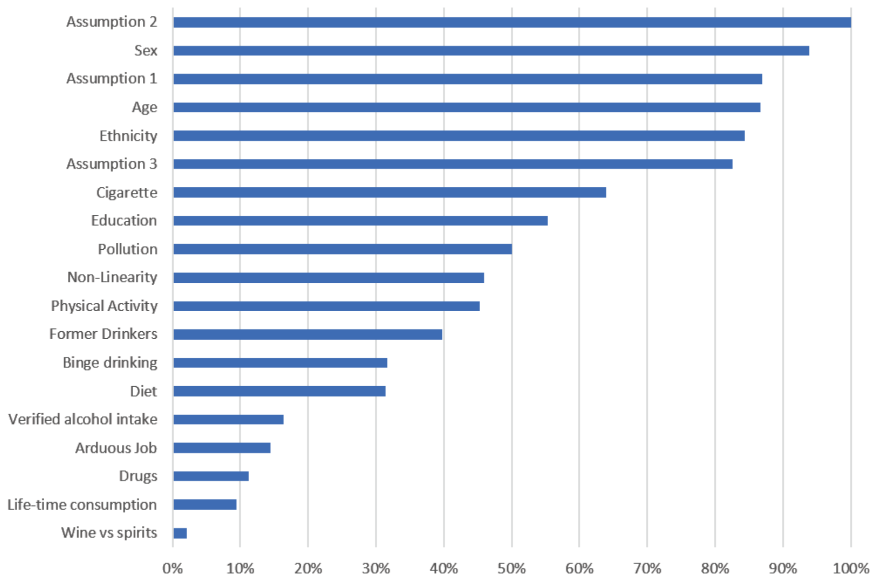
Note: Comparison of the SJR distribution between papers displaying at least one not significant results in the abstract and papers with only significant results. This analysis has been carried out on 3.217 papers out of a total of 6.763.

Figure 4: Distribution of the ”quality score”



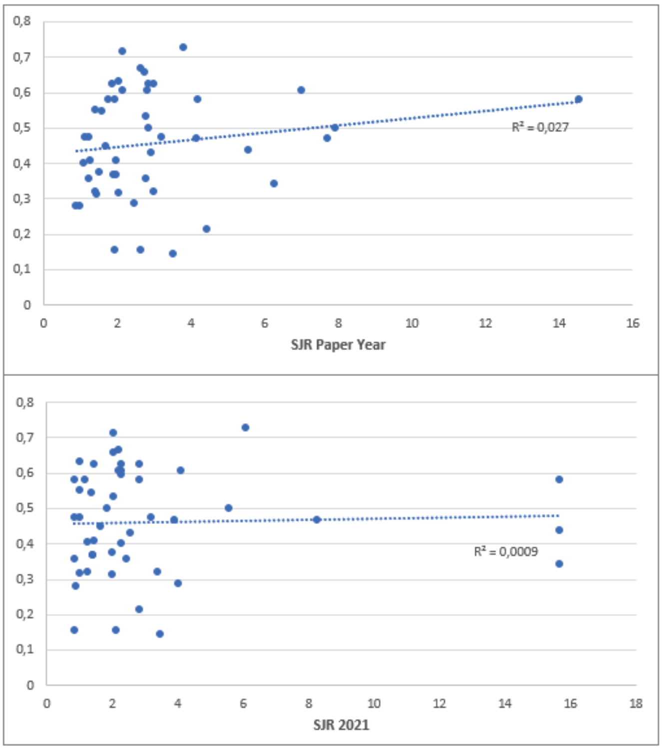
Note: Distribution of the ”quality score” values for the selected 49 papers, sorted in decreasing order.

Figure 5: Sources of bias in alcohol related papers



Note: Percentage of papers that appropriately analyze each specific source of bias when necessary. For instance, if a paper aimed at estimating the impact of alcohol consumption on the probability of car accidents, we do not consider variables such as cigarette smoking or physical activity.

Figure 6: The SJR and the "quality score"



Note: Association between the Scimago Journal Ranking, measured both in the year of publication and in 2021, and our "quality score".

Tables

Table 1: List of the 49 papers selected for the methodological analysis

Source	Paper
WHO report on alcohol (2018)	Cao et al. (2015)
	Dal Maso et al. (2016)
	Fergusson et al. (2009)
	Foster et al. (1988)
	Gmel et al. (2011)
	Gmel et al. (2013)
	Grundy et al. (2016)
	Henriksen et al. (2004)
	Kalichman et al. (2008)
	Leon et al. (2007)
	Leong et al. (2014)
	Manthey et al. (2017)
	Manthey et al. (2018)
	Rivara et al. (1993)
	Saxena et al. (2003)
	Schütze et al. (2011)
	Shield et al. (2018)
	Scott-Sheldon et al. (2014)
	Taylor et al. (2016)
	Zaridze et al. (2009a)
	Zaridze et al. (2009b)
CDC WS	Esser et al. (2022)
	Hess et al. (2015)
	Naimi et al. (2005)
	Stahre et al. (2014)
	Wen et al. (2012)
Mendelian randomization papers	Almeida et al. (2017)
	Au Yeung et al. (2013a)
	Au Yeung et al. (2013b)
	Cho et al. (2015)
	Cho et al. (2018)
	Christensen et al. (2018)
	Holmes et al. (2014)
	Jee et al. (2016)
	Jiang et al. (2020)
	Larsson et al. (2020)
	Lawlor et al. (2013)
	Millwood et al. (2019)
	Peng et al. (2019)
	Silverwood et al. (2014)
	Tabara et al. (2016)
	Tabara et al. (2017)
	Taylor et al. (2015)
	van Oort et al. (2020b)
	van Oort et al. (2020a)
	van Oort et al. (2021)
	Vu et al. (2016)
	Yuan and Larsson (2020)
	Zhao et al. (2019)

Note: Holmes et al. (2014) is also cited in the WHO report

Table 2: List and description of the 19 binary indicators and the computed "quality score"

Variable	Description
Cigarette use	Control for the effect of smoking
Education level	Account for differences in educational attainment
Dietary factors	Account for the effects of diet
Drugs	Account for the effects of drug use
Physical Activity	Account for physical activity
Job type	Account for the effects of sedentary or physically demanding jobs
Pollution	Account for differences in exposure to pollution
Age	Effects of age on health outcomes
Ethnicity	Account for differences in race or ethnicity among study participants
Sex	Account for differences in sex among study participants
Non-linearity	Assume a potentially non-linear relationship
Verified alcohol intake	Verify the accuracy of self-reported alcohol consumption data by comparing it to blood concentration
Binge-drinking	Account for the impact of excessive amounts of alcohol in a short period of time
Life-time consumption	Account for long-term alcohol consumption patterns
Alcoholic typologies	Account for the differential effects of various types of alcoholic beverages
Former Drinkers	Account for past alcohol consumption
Assumption 1 Mendelian	Association between the genetic variant and alcohol consumption
Assumption 2 Mendelian	Potential confounding factors associated with the genetic variant
Assumption 3 Mendelian	Potential direct effects of the genetic variant on health outcomes
Quality Score	The mean of all indicators

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