Low Risk Alcohol Consumption Thresholds

Update on the risks associated to alcohol consumption levels, consumption patterns, and the type of beverages

Part 2. Review of scientific evidence

REPORTS, STUDIES AND RESEARCH 2021
MINISTRY OF HEALTH

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Part 2. Review of scientific evidence

GOBIERNO DE ESPAÑA MINISTERIO DE SANIDAD

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1. Health risk assessments and low risk thresholds for average alcohol consumption

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Abbreviations

HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
IARC	International Agency for Cancer Research
ICD	International Classification of Diseases
SD	Standard Drink
SES	Socioeconomic Status
WHO	World Health Organization

Executive summary

Alcohol is responsible for over 200 health problems and it contributes significantly to the development of 40 specific diseases. Worldwide, alcohol consumption is responsible for 27.1% of cancer deaths in women and 18.9% of deaths among men over the age of 50. In Spain, alcohol is attributed 10% of total mortality and 27.7% of mortality due to traffic accidents. The health risk depends on the amount consumed. Usually, the greater the intake, the greater the risk. The objective of the working group was to define low risk alcohol consumption thresholds, by evaluating the impact of such thresholds on population mortality. To this end, the group performed two reviews of the literature focused on the relationship between average alcohol consumption and mortality. The first review focused on reviewing systematic reviews and meta-analyses. The second review focused on reviewing cohort studies free of the biases identified in the first review and published in the previous 5 years (starting in 2014).

The analysis of the systematic reviews and meta-analyses on average alcohol consumption and all-cause mortality provides biased information regarding their association. On one hand this is so because the primary studies included failed to differentiate between ex-drinkers and never-drinkers, which may overestimate the protective effect of alcohol consumption. On the other hand, "moderate" drinkers tend to be healthier and enjoy higher socioeconomic status (SES), important factors not always addressed in these studies. Likewise, one must also take into account that although it has been argued that certain amounts of alcohol may be associated to a lower risk of certain cardiovascular diseases under certain circumstances, this benefit would not compensate the increased risk of other cardiovascular diseases or cancer-related mortality alcohol is already associated with or to overall mortality.

For cohort studies published on or after 2014 to be selected for this review, they had to be free of the biases identified in the systematic reviews. Further, studies not performed in countries of similar sociocultural environment as ours and those presenting obvious conflicts of interest were excluded.

These studies have modified, to a great extent, the paradigm of the benefit of a "moderate" alcohol consumption. If we take into account the principle of precaution and take the most conservative levels of average alcohol consumption beyond which increases in mortality have been detected, we will observe that the most conservative figures obtained from systematic reviews match those of cohort studies published in recent years. Thus, we conclude that **low risk consumption thresholds** should be set at **20 g/day for men** and **10 g/day in women**, understanding that only no alcohol consumption is risk-free.

Introduction

1. Alcohol and burden of disease

Alcohol consumption is not only a very well established and conventional habit in our culture but it is also strongly associated to our traditions and celebrations. Drinking contributes to socializing, and we associate it with happy moments. These qualities may be considered positive; however, alcohol consumption is not risk-free. The risk depends on the amount, frequency, consumption pattern, and the drinker´s characteristics such as age, sex, and health status. Thus, it is important to be informed about the health risks associated with alcohol consumption.

About 7.4% of the adult population consume alcoholic beverages daily which may be an health issue.[1] Alcohol is an addictive substance which may lead to addiction and dependency if consumed often and even more so the greater the volume of alcohol of the beverage of choice. Alcohol consumption is responsible for over 200 health problems and injuries, and it contributes significantly to 40 specific diseases (ICD code 10) by increasing their risk. A significant portion of all preventable mortality and morbidity is attributed to alcohol consumption.[2,3]

In 2017 in Spain, it is estimated that 10% of the overall mortality and approximately 27.7% of mortality caused by accidents were due to alcohol consumption. Of all the victims of these accidents, 46% belonged to vulnerable groups: pedestrians, cyclists, and motorbike drivers (involuntary victims of alcohol).[4] Alcohol-associated morbidity includes digestive, psychiatric, neurological, and infectious (tuberculosis) conditions. It also contributes to different types of cancer, cardiovascular diseases (e.g., hemorrhagic stroke, heart failure, arrhythmias, cardiomyopathy), intentional injuries (e.g., suicides), non-intentional injuries (violence), social pathology (addiction), and family problems.[5] In addition, given that each gram of alcohol has 7 kcal, it is estimated that it may substantially contribute to the overweight and obesity epidemic. For instance, a small 250cc beer (referred to as “caña” in Spain) has 90 kcal, 70 of which come from its alcohol content.[6]

A 2018 study covering 195 countries and territories reported that, in 2016, alcohol consumption was the seventh risk factor for all-cause mortality (2,800,000 deaths) as well as for loss of disability-adjusted life years (DALYs). The study reported that alcohol was responsible for 2.2% of all female deaths and 6.8% of male deaths, both standardized by age. In the population between the ages of 15 and 49 years, alcohol consumption was the main risk factor for death. For those 50 and over, cancers represent an important proportion of total alcohol-attributable deaths, specifically 27.1% of total deaths in women and 18.9% for men. Of all causes of death, the main ones attributable to alcohol in this age group were: tuberculosis, traffic-related injuries, and self-inflicted harm. Other causes were traffic accidents, suicides, liver cirrhosis, cardiovascular diseases and different types of cancer. The same report indicated that the mortality risk for any cause, but especially for cancers, increased with higher alcohol intake levels, and the consumption level that minimizes health damage is zero.[7]

2. Alcohol and cardiovascular risk

A beneficial effect of small doses of alcohol on ischemic cardiopathy and thrombotic stroke has been reported. However, most studies on these biomarkers are observational in design and, in any case, these effects must be contextualized within the overall effects of alcohol consumption.[8] Between 2000 and 2014, systematic reviews and meta-analyses seemed to conclude that alcohol consumption conferred a clear benefit regarding cardiovascular and all-cause mortality.[9] However, we must take into account that the relationship between alcohol consumption and cardiovascular risk is a complex one. Several biases have been described which may account for this observed association as we discuss later on in this report. In fact, we know that binge drinking increases the risk for heart attack (INTERHEART, 2014).[10] Additionally, intakes of 30 g/day increase the risk of many cardiovascular diseases such as hypertension, atrial fibrillation, alcoholic cardiomyopathy, or cardiac failure. Smyth and colleagues reported that intakes above 10 g/day in women or 20 g/day in men reduced the risk for heart attacks by 24% but the risk for cancer increased by 51%.[11] Wood et al., observed that individuals consuming more than 28.5 g/day on average increased their risk for stroke by 14%, angina by 6%, cardiac failure by 9%, hypertension by 24%, and arrhythmia by 15%. In contrast, a 6% reduction in myocardial infarction was observed.[12] The protective effect against stroke has been observed with very low doses under 20 g/day.[13] Despite the results described above showing a slight reduction in mortality caused by ischemic cardiopathy, the cardiovascular benefit is far outweighed by excess mortality by all the other causes.[2] Further, most individuals can reduce their cardiovascular risk in a safe and effective manner by increasing physical activity and with a healthy diet. Thus, the avoidance of binge drinking and the concept that the best for our health is to abstain from alcohol or consume it in amounts much lower than those accepted as normal in Spain are two ideas that should be emphasized and circulated among the population.

3. Alcohol and Cancer

To understand the complexity involved in the alcohol-disease relationship is key to delve into studies on alcohol and cancer. As mentioned above, although some of them show that small amounts of alcohol may reduce the risk of heart attacks or diabetes, those same amounts increase the risk of other diseases such as some of the most common cancers in the population at large (e.g., colon, esophagus, breast). Based on estimates, in the United States (U.S.) alcohol is responsible for 5.6% of all cancer mortality, i.e., 87,000 preventable deaths every year.[14] Some studies have created confusion and doubts by emphasizing alcohol´s "beneficial effects" on certain "biomarkers" which are nothing more than intermediate variables with no relationship with overall mortality. These studies hide the carcinogenic effect of the main alcohol metabolite, acetaldehyde, which is proven to be associated to the onset of different types of cancer.[15] Although the average population risk in absolute terms is low, alcohol is a carcinogen and, thus, an overall global protective effect does not exist. The risk of digestive cancer associated to alcohol consumption increases by 10-30% every two Standard Drinks (SDs) of alcohol consumed a day[1]. The risk for esophageal cancer increases by 26% with doses up to 12.5 g/day and by 79% with doses

[1] 1 SD in Spain= 10 g

between 12.6 and 49.9 g/day. Liver and colon cancer risks increase by 16% with alcohol intakes of or above of 15-30 g/day. Intakes below 25 g/day have already been associated to an increased risk for breast cancer.[16]

As part of the **European Prospective Investigation into Cancer and nutrition** (EPIC) study, it was observed that 10% of cancers in men and 3% of cancers in women were associated significantly to alcohol consumption; these are cancers with an average 5-year survival rate of 50%. According to EPIC´s assessments and 2017 mortality data from the Spanish Society for Medical Oncology (SEOM for its Spanish abbreviation), we could expect 1,343 alcohol-related cancer deaths in women (3%) and 6,850 in men (10%), for a total of 8,192 cancer deaths attributable to alcohol based on the average real alcohol consumption in Spain.[17]

According to the **International Agency for Cancer Research (IARC)**, alcohol is a Group A carcinogen for which there is no safe exposure level.[18,19]**.**

Table 1. Evidence of the association between alcohol consumption and cancer (IARC)*

Degree of Association	International Agency for Research on Cancer (IARC)
Sufficient evidence in humans	Oral cavity, pharynx, larynx, esophagus, colon and rectum, breast (female), liver and biliary duct
Limited evidence in humans	Pancreas

*Adapted from the International Agency for Research on Cancer: List of Classifications by cancer sites with sufficient or limited evidence in humans, Volumes 1 to 125a[20]

4. Alcohol and warnings about alcohol consumption in Spain

Alcohol consumption terms such as "moderate," "prudent," "social," and "responsible" are misleading and confusing; they are the product of marketing strategies rather than public health policies. For the last few years, national guidelines in this field have been using the concept of "low risk" consumption given that, as explained above, we know that for certain gastrointestinal diseases, cancer, and injuries, there is no safe consumption level. [5] Nevertheless, variability in these recommendations exists due to the use of differences methodologies and conceptualizations of what "low risk" means. Inevitably, this has created some confusion among individuals as well as among health professionals. Thus, there is a growing need for a consensus in the definition of low risk consumption and for making it widely known to the population.

We need to differentiate between low risk levels at the population level from the specific consumption levels at which health professionals should intervene and recommend a reduction in consumption or abstinence at the individual level.

The purpose of this report is not telling individuals what to do regarding their drinking or not. Here we collect scientific evidence referring to average data at the population level. Estimating the specific risks of any one individual corresponds to their usual health providers. The responsibilities of the Health Services Institutions, as established in art. 3 of the General Public Health Act, is to inform society of the effects related to the consumption of certain amounts of alcohol so that each person gains a better understanding of the

risks assumed in the short/long term if they consume any type of alcoholic drink. Additional responsibilities include developing public policies to protect the health of the population.[21] In order to exercise real freedom of choice one must have access to complete and true information about the potential consequences of certain health habits for oneself and others, as well as information about the environments where the healthier options are the easiest to choose.

Objective

The objective of the working group was to establish alcohol consumption thresholds which could be considered low risk, and provide such information to the population and health professionals.

Review of the evidence

Using two types of scientific reviews, we reviewed average alcohol consumption levels beyond which an increase in global mortality is reported in scientific publications:

1. Review of systematic reviews with or without meta-analysis (umbrella review).
2. Review of cohort studies controlling for bias, published from 2014 on.

Characteristics of the articles included

Searches for relevant articles were performed in databases Medline, Embase, and PsycINFO, with no language restrictions, using the different keywords grouped in three filters: alcohol (and related keywords), systematic review or meta-analysis, and mortality. For the first review we also used the filters "systematic review" and "meta-analysis." In Annex I and II there is detailed information on the search strategies.

For the review of systematic reviews with or without meta-analysis (Review 1) we identified all reviews published up to February 2019, regardless of publication date. The Cochrane Database was also examined. For the review of cohort studies (Review 2), we chose works published between 2014 and May 2019.

In Review 1 and Review 2 we included all works addressing the relationship between global mortality and morbidity with levels of alcohol consumption. Information regarding levels of intake were collected in the form of SDs and/or grams; although, given the regional variability of SD definition, we converted all consumption data into grams of alcohol. Articles selected for either Review 1 or 2 included, in addition to the aforementioned alcohol data, overall mortality and/or morbidity as dependent variables. Those data produced results in the form of Hazard Ratios or incidence.

The exclusion criteria for any of the two Reviews were:

- Studies focused on certain pathologies and/or populations and/or patients with a pre-diagnosed condition (e.g., HIV+ status, hypertension) instead of the general population.
- Studies on the efficacy of certain treatments on patients with alcohol-derived diseases.
- Studies of traffic accident deaths.
- Studies examining survival exclusively.
- Studies of the impact of changes in alcohol-related policies (e.g., price, availability).
- Non-systematic reviews, narratives/critical reviews, or pathophysiological reviews.

Selection of reviews or cohort studies and data extraction

A member of the research team reviewed the titles and abstracts of the articles identified by the databases search, selecting those meeting both inclusion and exclusion criteria.

For each article, data on publication year, author(s), country(ies) involved, number of people included in the research, time of follow-up, range of alcohol amounts examined and their association to mortality or morbidity provided as Hazard Ratios or Risk Ratios were collected. Specifically, for each single study, we extracted the exact amount of alcohol intake beyond which a significant association with increased all-cause mortality was identified (Tables 3 and 4).

Results and discussion of the reviews selected (Review 1)

After eliminating duplicates across databases, we identified 516 articles, of which 63 were systematic reviews with or without meta-analysis. Of these, 9 met our inclusion/exclusion criteria and provided mortality data (Table 3).

Alcohol levels and mortality

The reviews selected in the previous step were published between 1996 and 2017. Primary data came from a diverse set of countries with a clear overrepresentation of the United States; only two reviews included data from Spain. The number of studies included in the reviews ranged between 9 and 87, with 27 being the median. Reviews were performed on cohort studies with follow-ups ranging between 10 and 15 years, with populations between 62,950 and 3,998,626 people.

According to the inclusion criteria, all selected reviews provided risk measures; however, there were articles with slightly different objectives and were considered separately.

Di Castelnuovo and colleagues start off with the idea of the existence of a specific alcohol intake dose associated to all-cause mortality. After reviewing 34 cohort studies up to 2005, they established the doses to be 38 g/day for men and 18 g/day for women.[22]

In their respective reviews White and Burger et al., determine a low risk level of alcohol consumption. White sets the low risk level at 9.9 g/day for men based on the U.S. studies and at 16.6 g/day based on the British studies. For women, the level is set at 3.7 g/day based only on the U.S. studies.[23] In contrast, Burger and colleagues,[24] set the "tolerable upper alcohol" or low risk intake level at 19 g/day for men and 10 g/day for women. The remaining 6 meta-analyses set risk consumption thresholds (beyond which a significant increase in mortality risk was observed at $p<0.05$) somewhere between 20 and 75 g/day for women and between 30 and 90 g/day for men.

The non-drinker control groups, upon which risk levels of drinkers are established, include ex-drinkers and individuals whose health conditions keep them from drinking. For this reason, the supposedly protective factor of alcohol as well as the thresholds reported by some studies should be questioned and re-examined.[25,26] Four of the systematic reviews reported alcohol intakes associated to a reduction in mortality risk, although two of the meta-analyses (the two most recent ones) pointed out to a bias common to the studies included in all the reviews.[27-30]

Considerations

The most relevant finding from this review of systematic reviews is that they report the figures provided by the meta-analyses, figures beyond which an association between alcohol intake and an increase in mortality is found. While the specific numbers are related to greater mortality, it does not mean necessarily that mortality is not elevated for intakes below those figures. On the one hand, it is common to find a positive association with lower figures, though not significant. On the other hand, sometimes authors of systematic review include only a specific range of alcohol intake, which impedes the inference of risks for other intake levels.

However, we cannot establish a low risk threshold for alcohol consumption beyond which mortality and/or morbidity significantly increases based solely on reviews of systematic reviews and meta-analyses. Findings in relevant systematic reviews support the existence of important biases in the primary studies. This calls for a new approach, e.g., reviewing only studies free of those biases. Our review of cohort studies is our attempt at such approach.

The analysis of the systematic reviews and meta-analyses on usual consumption and mortality offers a clear picture of the many limitations of the primary studies the results are based on. Many of these studies overestimate the cardiovascular protection and underestimate the excess mortality due to at-risk consumption.[25,31] Further, the samples used in these studies are not always representative of the overall population but of middle class groups, failing to include low SES vulnerable groups as well as high SES individuals. Also, studies based on a specific country may not take into account region-specific genetic factors such as genes predisposing the individual to certain alcohol-related diseases.[5]

Several of these reviews find "moderate alcohol consumption" to be a protective factor. Many authors have pointed out that this finding may be the result of incorrect classification of ex-drinkers as non-drinkers and sometimes the combination of non-drinkers with occasional drinkers. The relationship between two variables does not automatically indicate the direction of the association or, in other words, one may argue that healthy individuals are the ones practicing a "moderate" consumption rather than a moderate consumption improving health. "Moderate" drinkers tend to be healthier and of higher SES. Further, in certain occasions results have not been adjusted for important lifestyle factors such as diet or physical activity. For instance, in one study non-drinkers presented with unfavorable levels in 27 out of 30 cardiovascular risk factors, too high a number of factors to adjust for statistically.[32]

Many of the studies included in the systematic reviews and meta-analyses tend to include biases not usually addressed, such as case selection bias, problems in the classification of categories, or lack of consistency between results and conclusions.[33]

Table 2. Summary of biases observed in publications finding a protective effect of alcohol intake on cardiovascular health

1) Bias of classification (combining ex-drinkers and non-drinkers)
2) Bias by omission of binge drinking
3) Bias by omission of confounding variables (SES, physical activity, and diet)
4) Bias of selection and classification (confounding cause-specific mortality with overall mortality)
5) Publication bias (overrepresentation of studies on cardiovascular risk)
6) "Incentivized" publication bias (conflicts of interest with industry)

In addition, it has been shown that studies funded by the industry tend to distort the research objectives and priorities.[34] The commercial activities of the alcohol industry present an obvious conflict of interest, as their interests are opposite to those of public health Any such industry funding may influence on the independence, objectivity, integrity, and credibility of the studies, as pointed out by the International Network on Brief Interventions for Alcohol & Other Drugs.[35]

Table 3. Meta-analysis/selected systematic reviews. Alcohol consumption levels and overall mortality

Year[1]	First Author	Objective/Main result	Follow-up	No. Studies and countries[2]	Deaths	Risk Threshold[3]	Relative Risk (95%CI)[4]	Main Limitation
1996	Holman[27]	All-cause mortality risk related to alcohol consumption	1,084,733 people/ 11.8 years	16: U.S. (11) Europe (5)	122,381	M >40 g/d W >20 g/d	1.06 (1.03-1.10) 1.13 (1.10-1.16)	Data NOT applicable to those under 35. No distinction between abstainers and ex drinkers
1999	White[23]	Alcohol consumption level linked to lowest mortality	Between 8 and 23 years	20: U.S. (10) UK (3) Other European (4) Japan (1) Australia (1)	139,048	M: U.S.: 69.3 g/w (9.9 day). UK 116.1 g/w (16.6 g/d) W: U.S. 26.1 g/w (3.7 g/d)		No exact data on increased risk
2003	Gmel[28]	Relationship between mortality and alcohol consumption: the influence of different variables.[α]	132 months median follow-up	50: Mostly U.S.		M: >40-70 g/d W: >30-50 g/d	1.04 (1.01-1.07) 1.40 (1.34-1.47)	Data from original articles confusing. Data differentiate between abstainers and ex drinkers
2004	Burger[24]	Determine maximum risk reduction point of alcohol intake	Data not available	27: Mostly U.S.		M: >19 g/d W: >10 g/d	Thresholds correspond to the "maximum risk reduction point"	Overrepresentation of U.S. sources,
2006	Di Castelnuovo[22]	All-cause mortality risk in relation to alcohol consumption	1,015,835 individuals/ 12.4 years	34: U.S. (9), Japan (5) Australia (2) Europe (18)		M: >38 g/d W:>18 g/d	"reversion point"	No distinction between abstainers and ex drinkers
2015	Jayase-kara[29]	All-cause mortality risk in relation to alcohol consumption	62,950 individuals/ 13 years	9: U.S. (4), Europe (5)	10,490	30-59 g/d and > 40 g/d	1.19 (0.89-1.58)*	Only male data
2014	Wang[30]	All-cause mortality risk in relation to alcohol consumption, women vs. men	2,424,964 individuals/ 11.3 years	24: U.S. (8), Asia (6) Australia (3), Europe (7)	123,878	M: 90 or more g/d W: 75 g/d	1.36 (1.02-1.80)* 1.74 (1.23-2.47)	All-cause mortality risk of women vs. men was 1.52 (95% CI: 1.01-2.29), 75 g/d. No distinction between abstainers and ex drinkers
2016	Stockwell [25]	All-cause mortality risk in relation to alcohol consumption: Assessing possible bias of misclassification of ex drinkers/abstainers.	3,998,626 individuals/ 13.4 years	87: U.S., Europe, Australia, Japan, China, and India	367,103	Global: 45-65 g/d	1.24 (1.12-1.37)*	The article itself questions the reliability of the stated self-reported data of the articles reviewed
2017	Stringhini [26]	Life-years lost to alcohol consumption and the contribution of SES factors to consumption	12,025,208 person-years	48: U.S. (36), Australia (1), Europe [one from Spain] (7)	161,524	M: >3 units/d W: >2 units/d	1.50 (1.38-1.64)** 1.69 (1.49-1.92)**	U.S. articles overrepresented due to inclusion criteria

1. Among current alcohol consumers in high income countries, the lowest risk threshold for all-cause mortality was approximately 100 g/week.

2. Risk starts at 20 SD/week for men and 10-15 for women.

3. Increase in mortality with consumption levels above 12 g/d for women and 24 g/day for men.

y.o.: years old; g: grams; d: day; w:week; M: men; W: Women; HR: Hazard Ratio; CI: Confidence Interval

* No sex specified

Results and discussion of the prospective multiple cohort studies with bias reduction (2014-2019) (Review 2)

After the review of systematic reviews and discussion of results, we decided to carry out our own systematic review including only those cohort studies published from 2014 on and that managed to minimize all those biases mentioned above. We chose 2014 because it is the year in which the field, as a whole, points out many of the biases discussed. We included those cohort studies which main objective was to study the relationship between average alcohol consumption and overall mortality. In addition to meeting all the inclusion/exclusion criteria discussed in the methodology section, we excluded cohort studies presenting conflicts of interest with the pharmacological or alcohol industry and those studies carried out in Asiatic populations.

After deleting duplicates, we selected 670 cohort studies published between January 2014 and May 2019. Of these, 93 examined the relationship between all-cause mortality and alcohol consumption. And 67 of these 93 studies provided overall mortality data. Upon close inspection, 10 of the articles met our inclusion and exclusion criteria. None of these 10 studies used ex-drinkers combined with never-drinkers as the reference group. Instead, they classified as never-drinkers only those individuals who have never consumed alcohol in their lifetime. [11,12,31,36-42]

However, in some cases, the population of reference was the group of occasional drinkers, which complicates the drawing of conclusions. The results yielded by these studies are adjusted by relevant confounding variables such as smoking, body mass index, and SES. When data were not provided in grams, we converted SDs into g/day or g/week.[43,44] A summary of the studies included in this section of the review follows **(Table 4).** Regarding overall mortality, from each of the selected studies we obtained those thresholds beyond which overall mortality increased. Although inclusion criteria eliminated studies from different geographic environments, results came from a very heterogeneous set of populations, countries, and age groups; thus, meta-analysis of these data is not advisable.[12,42] Alcohol intake thresholds beyond which mortality increased ranged between 20 and 60 g/day for men and between 12 and 20 g/day for women.

Considerations

In light of these results, low risk alcohol consumption levels may be defined as those thresholds beyond which any higher consumption significantly increases mortality risks, while not necessarily meaning that lower consumptions do not also increase mortality risk. Following the precautionary principle and based on the most conservative figures for average alcohol consumption beyond which an increased overall mortality has already been observed, **low risk alcohol consumption should be set at 20 g/day for men and 10 g/day for women, while still assuming there is no such thing as zero risk.**

These data come from the review of evidence published in recent years, but they are also consistent with the figures provided in other countries such as Portugal (24 and 16 g/day for men and women, respectively); Germany or Italy (24 and 12 g/day respectively) and even France (20 g/day for both sexes) or Norway (20 and 10 g/day, respectively). These thresholds match the most conservative ones obtained from Review 1, if momen-

tarily ignoring its biases. Further, they also support the recommendations of some of the most relevant recently published studies such as Shield et al.[5] This article concludes that, in order to minimize risk, European low risk thresholds should be 15-20 g/day for men and 8-10 g/day for women. Kunzmann et al. also conclude that the low risk dose should be under 2 U.S. SDs (i.e., 28 g) for men and 1 SD (14 g) for women without implying any protective effect below those amounts.[45] These sex differences in consumption are determined by the differences in the alcohol dehydrogenase levels and the ability to metabolize alcohol.[46]

Table 4. Summary of cohort studies with minimized biases (2014-2019)

First author/ year	No. individuals	No. Countries	Sex/Age	Median follow-up (years)	Ex drinker Bias	Mortality increases (p<0.05) if this amount exceeded	Low risk threshold/ Amount with minimum mortality risk	Total mortality (HR:95%CI) below the threshold
Wood 2018[12]	599,912	19	Both >57 y.o.	9	No	17-21 g/d	14.2g/d[1]	HR=1 Control Group
Ferrari, 2014[42]	380,453	10 EU (Spain included)	Both >53 y.o.	12.6	No	30 g/d	5-15 g/d	M: HR: 0.93 (0.87-0.99)
Smyth, 2015[11]	114,000	12 from 4 continents	Both Adults	4.3	No	M: 30g/d W: 20g/d High Consumption		M: HR: 0.97 (0.87-1.09) W: HR: 1.31 (1.04-1.66)
Knott, 2015[36]	53,000	United Kingdom	Both >50 y.o.	6.5-9.7	No	No evidence of association to greater mortality	M: 22g/d W: 11g/d [2]	Men (50-64 y.o.) HR: 0.49 (0.26-0.91); Women (>64 y.o.) HR: 0.77 (0.63-0.94)
Perreault, 2017[37]	36,370	United Kingdom	Both >40 y.o.	9.7	No	M: 24 g/d W: 16 g/d,	M: 16 g/d W: 8 g/d Minimum Risk Value	HR: 1.10 (1.00-1.20)
Goulden, 2016[31]	24,000	U.S.	Both >50 y.o.	4	No	35 g/d (ref. never drinkers)	14.2 g/d	Me: HR: 1.04 (0.92-1.18) [ref. occasional drinkers] Women: HR: 1.0 (0.90-1.12)
Bobak, 2016[38]	34,304	4 (East Europe)	Both 45-69 y.o.	7	No	60g/d y 20g/d, for men and women	M: 10g/d W: 5g/d	HR= 1 Control Group
Luksiene, 2017[39]	6,729	Lithuania	Both 35-64 y.o.	31	No	M: 20 g/d [ref. moderate intake]	20g/d	HR=1 Control Group
Licaj, 2016[40]	48,249	Sweden	W: 30-49 y.o.	11	No	15g/d (Null Association) p>0.05	15g/d (Null Association) All p>0.05	0.90 (0.70-1.13)
Midlöv, 2016[41]	10,766	Sweden	W: 50-59 y.o	15	Yes	12g/d[3]	12g/d	HR=1 Control Group
Medians:						Global*: 23-25 g/d M: 24 / W: 20	Global*: 14.2 g/d M: 19 / W: 10.5	

1. Among current alcohol consumers in high income countries, the lowest risk threshold for all-cause mortality was approximately 100 g/week.
2. Risk starts at 20 SD/week for men and 10-15 for women.
3. Increase in mortality with consumption levels above 12 g/d for women and 24 g/day for men.

y.o.: years old; g: grams; d: day; w:week; M: men; W: Women; HR: Hazard Ratio; CI: Confidence Interval

* No sex specified

Conclusions

- There is no alcohol consumption level that can be considered beneficial to our health. The intake level that minimizes harm is zero.
- No professional must recommend alcohol consumption for any health issue or condition, even if the risk for a specific disease may decrease slightly, the patient´s prognosis would not improve.
- Low risk alcohol consumption thresholds are defined as those beyond which there is evidence of a significant mortality increase.
  Taking into consideration the physiological differences between the sexes and their different capacity to metabolize alcohol, **low risk** alcohol consumption thresholds should be set at **20 g/day for men and 10 g/day for women**, while assuming that only zero consumption carries zero risk.

Note: 1 Standard Drink (SD) of alcohol in Spain is equivalent to 10 g which equals the content of half a glass of wine of 100cc and 13% alcohol content, 1 250cc glass of beer with 5% alcohol content, or 30cc of spirits with 40% alcohol content. The alcohol content in grams is calculated for each alcoholic beverage using the following formula: **Amount of cc x percent alcohol content x 0.8/100.**

Annex I. Methodology for evidence selection: Review 1 (systematic revisions with or without meta-analysis, Umbrella review)

We located relevant articles using the following search strategy (Search chains):

A) Pubmed:

Phase 1: Search for reviews/meta-analysis addressing alcohol and mortality:

#1 "Alcohol-Induced Disorders"[Mesh] OR "Alcohol-Related Disorders"[Mesh] OR "Alcohol Drinking"[Mesh] OR "Ethanol"[Mesh]
2"Mortality"[Mesh] OR "mortality" [Subheading] OR "Mortality, Premature"[Mesh]
3 "Network Meta-Analysis"[Mesh] OR "Meta-Analysis" [Publication Type]))
4 "Systematic Review" [Publication Type] OR "Systematic Reviews as Topic"[Mesh] OR "Root Cause Analysis"[Mesh]
Search: #1 AND #2 AND (#3 OR #4): 151 articles (51 since 2013)
Phase 2: DALY instead of mortality.
#5 "Global Burden of Disease"[Mesh] OR DALY OR morbidity OR cancer OR stroke OR cirrhosis
#6 Search #1 AND #5 AND (#3 OR #4): 150 articles
(((((("Global Burden of Disease"[Mesh] OR DALY OR morbidity OR cancer OR Stroke) AND ("Alcohol-Induced Disorders"[Mesh] OR "Alcohol-Related Disorders"[Mesh] OR "Alcohol Drinking"[Mesh] OR "Ethanol"[Mesh])) AND ((("Systematic Review" [Publication Type] OR "Systematic Reviews as Topic"[Mesh] OR "Root Cause Analysis"[Mesh])) OR ("Network Meta-Analysis"[Mesh] OR "Meta-Analysis" [Publication Type])))) AND ((((("Mortality"[Mesh] OR "mortality" [Subheading] OR "Mortality, Premature"[Mesh])) AND ("Alcohol-Induced Disorders"[Mesh] OR "Alcohol-Related Disorders"[Mesh] OR "Alcohol Drinking"[Mesh] OR "Ethanol"[Mesh])) AND ((("Systematic Review" [Publication Type] OR "Systematic Reviews as Topic"[Mesh] OR "Root Cause Analysis"[Mesh])) OR ("Network Meta-Analysis"[Mesh] OR "Meta-Analysis" [Publication Type]))))
#7 Added without terms MESH: Mortality AND Alcohol AND ("Systematic review" OR "Metaanalisis" OR "meta-analysis")
Search: #6 OR #7: 168 articles

B) PsyINFO: ("systematic review" OR meta-analysis) AND (mortality AND alcohol): 165. C) Cochrane: "alcohol": 133 reviews. No results about mortality nor morbidity, mainly about interventions

D) EMBASE: #1 Mortality OR morbidity (Keywords), #2 Systematic Review OR Meta-analysis (Keywords), #3 Alcohol (Keyword)

#1 AND #2 AND #3: 259 results

Annex II. Methodology for evidence selection: Review 2 (cohort studies 2014-2019)

We located relevant articles using the following search strategy:

A) Pubmed:
#1 “Alcohol-Induced Disorders”[Mesh] OR “Alcohol-Related Disorders”[Mesh] OR “Alcohol Drinking”[Mesh] OR “Ethanol”[Mesh]
#2”Mortality”[Mesh] OR “mortality” [Subheading] OR “Mortality, Premature”[Mesh]
#3 “Cohort Studies”[Mesh] OR “cohort”
Limited to: Research on humans published 01/01/2014 onward
Search: #1 AND #2 AND #3

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2. Health risk assessment and low risk thresholds for binge drinking

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Abbreviations

95% CI	95% Confidence Interval
EDADES	*Encuesta Domiciliaria sobre Drogas y Alcohol en España* (Home Survey on Drugs and Alcohol in Spain)
EESE	*Encuesta Europea de Salud en España* (European Health Survey in Spain)
EHIS	European Health Interview Survey
ENSE	*Encuesta Nacional de Salud en España* (Spanish National Health Survey)
ESTUDES	*Encuesta Estatal sobre Uso de Drogas en Enseñanzas Secundarias* (National Survey on Drug Use in Secondary School)
FASD	Fetal Alcohol Spectrum Disorders
HDL	high density lipoprotein
LDL	low density lipoprotein
NIAAA	National Institute on Alcohol Abuse and Alcoholism
SD	Standard Drink

Executive summary

Binge drinking is characterized by the intake of large amounts of alcohol over a short period of time or session. A substantial portion of these drinkers report a low risk average consumption and, thus, they could easily be erroneously classified as low risk drinkers. To make matters worse, the negative consequences of binge drinking are equivalent, or worse in some cases, to those associated to at-risk average consumption.

To identify this pattern, and assess its frequency, characteristics, and effects in a consistent manner, it is necessary to pay close attention to certain methodological issues. These issues are, mainly, defining the amount of alcohol consumed during each session, identifying the actual drinking session, and circumscribe the temporal period established as the reference. Also, it is necessary to establish sex-specific thresholds and adjust the estimates according to average consumption and other confounding variables (e.g., other lifestyles, sociodemographic variables).

Both acute and chronic effects associated to binge drinking are serious and affect the drinkers themselves and other people proportionally to the amount consumed in each binge episode. Specifically, this drinking pattern is clearly associated to a myriad of cardiovascular problems, alcohol abuse and dependency, disturbances in neurological development, accidents, violence or unsafe sex, among others, even in sporadic binge drinkers.

For the reasons presented above, we cannot determine a safe or low risk threshold for this consumption pattern which, by definition, should always be discouraged. Binge drinkers should be asked to consider reducing the frequency as well as the amount of alcohol consumed in each binge. Binge drinking research is key to the identification of all at-risk drinkers and typify the health impact of this pattern, both independently as well as associated to at-risk average consumption.

Introduction

Binge drinking: concept and assessment

According to the World Health Organization, binge drinking is defined as the intake of large amounts of alcohol over a short period of time dedicated deliberately to drinking.[1]

Binge drinking implies consuming large amounts of alcohol in a short time span (a drinking episode), usually reaching alcoholic intoxication. It is a common practice in Anglo Saxon and north European countries, where it is known as heavy episodic drinking, risky single occasion drinking, and other names. Binge drinking is the most common name in the international scientific literature.

Unfortunately, there is no consensus in its operational definition which leads to great heterogeneity among studies. To establish one such definition, we should consider the amount of alcohol consumed as well as the definition of episode or drinking session, or any temporal reference used to define this drinking pattern. However, there is no scientific consensus currently for any of these parameters.

The threshold proposed in 2004 by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) for defining binge drinking episodes is one of the most commonly used; it reads as follows: "the consumption, during one same drinking session, of ≥5 standard drink (SD) for men and ≥4 for women, in the last 2 weeks". They arrived at this amount by estimating the alcohol intake that would elevate the concentration of blood alcohol to 0.08 g/dL, causing alcoholic intoxication.[2] Some studies consider this definition to be too restrictive, arguing that there are individual and contextual differences (e.g., speed of consumption, body mass, food consumed) that influence alcohol concentration, and their authors suggest using higher cut points. Along these lines, other researchers propose to also use qualitative definitions (e.g., "drunkenness," "intoxication") which subjectivity would make comparisons and causal inferences even more complex.

The United Kingdom adopted a different objective definition, more easily adaptable to the official recommendations based on the usual consumption typical of each country: "the intake, in one drinking session, greater than double the daily alcohol consumption considered low risk." In that country that would equal ≥8 SDs for men and ≥6 SDs for women.[3]

More recently, some authors have tried to estimate the most adequate threshold based on the best known acute effects of this consumption pattern, paying attention to the incremental negative effects (more frequent and serious consequences the larger the threshold is).[4] This illustrates the importance of considering not only the threshold, but also the intensity or amount of alcohol consumed in each episode, which would remained unknown with a dichotomous or a not very restrictive definition of binge drinking. Other authors have established a more restrictive cut point (50 g and 40 g of alcohol for men and women, respectively), which could be useful to predict some of the most common acute consequences, but could also turn out not specific enough to identify the most serious consequences of this drinking pattern.[5]

A binge drinking definition must differentiate the established threshold by sex due to the aforementioned existing differences in body mass and ethanol metabolism which influence its effects. Nevertheless, often used tools for screening at-risk alcohol consump-

tion as AUDIT, or institutions such as WHO, continue to use the single threshold of 60 g of ethanol for both sexes.[6-8]

Another source of heterogeneity in the definition of binge drinking comes from the differences in the SD across countries which are often ignored when comparing proposed definitions internationally. For instance, in the United States, an SD equals 14 g of pure alcohol, thus their binge drinking threshold of 5/4 SDs (for men and women, respectively) corresponds to ≥70 and ≥56 g of pure alcohol. In contrast, this same 5/4 SDs threshold would amount to ≥50 g and ≥40 g in Spain given that our SD refers to 10 g of pure alcohol. The United Kingdom´s threshold of 8/6 SDs corresponds to ≥64 g and ≥48 g of pure alcohol, for men and women respectively, given the 8g of alcohol assigned to each of UK´s SDs. U.K.´s definition is actually very similar to the one proposed by the NIAAA.

It is also important to consider the type of drinks consumed during binge drinking episodes. At the very least we should differentiate between low- and high-alcohol content drinks, and then convert that content into grams of ethanol. This is even more important given that most binge drinkers consume amounts of alcohol that greatly exceed the thresholds we use to define this pattern.[9,10]

The time frame used to classify binge drinking is also as relevant. What we understand as "episode or drinking session" may vary greatly across countries. This definition depends on the most common alcohol consumption habit in each culture: a couple of hours of drinking in Anglo Saxon or north European countries (with a typically more sporadic and concentrated alcohol consumption) versus several more hours of regular and social consumption found in Mediterranean countries. A similar issue refers to how far back do we enquire about these episodes of intense drinking. Typically, questions refer to a range between the previous "2 weeks," "30 days," or "12 months." The chosen criteria will obviously influence the final estimated prevalence, although important negative effects have been described for binge drinkers, regardless of which period of time was used to classify them as such. In any case, in order to compare across studies, it is important to consider these differences.

In Annex I we summarize and compare how the different Spanish systems of epidemiological information currently address this assessment as well as the differences in binge drinking measurement across countries and institutions worldwide.

Study objective

The objective was to carry out a review of reviews (narrative, systematic, or meta-analysis) published in the previous 5 years to identify evidence related to the health effects of binge drinking. The search strategy for the articles is described in Annex 1.

Review of the evidence: health effects of binge drinking

Binge drinking is associated to substantial negative impacts for the drinker, other people, and society as a whole. These impacts are proportional to the amount of alcohol consumed in each binging episode and the frequency of the episodes. The effects of binge drinking are independent of average consumption and comparable in magnitude and relevance to the effects traditionally attributed to at-risk average consumption, even if the binge drinking is a sporadic practice.

Figure 1. Comprehensive model of the effects associated to alcohol consumption (based on Rehm et al.)[11]

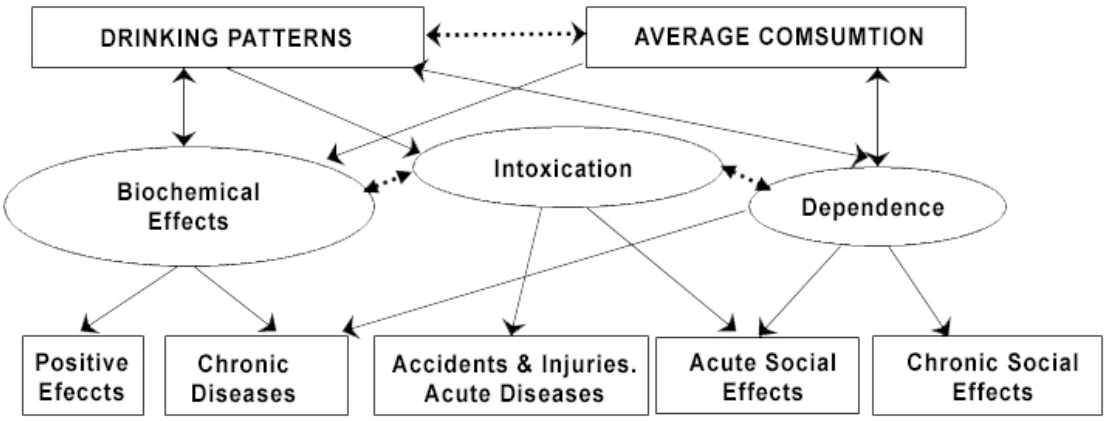
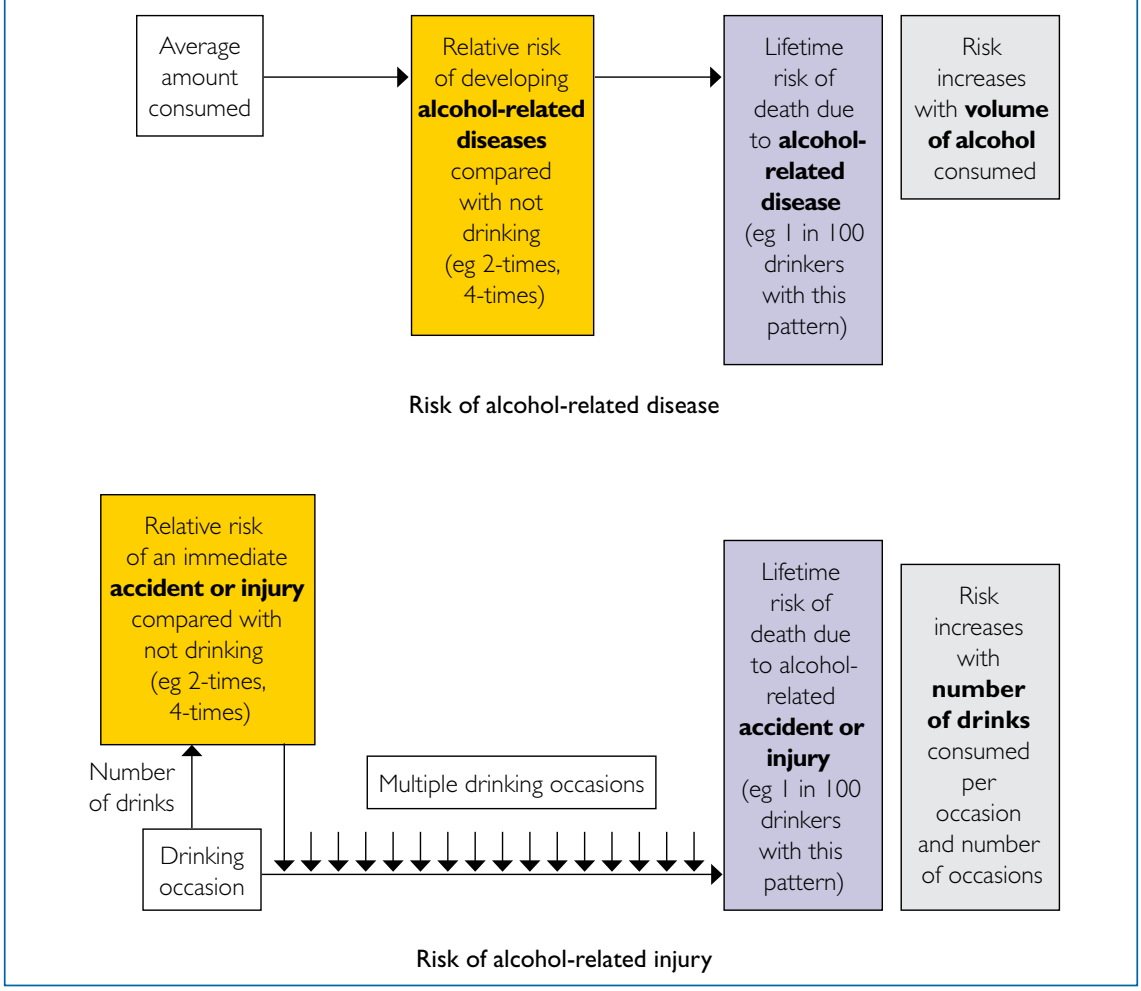


Figure 2. Alcohol-related risks for different patterns of drinking (Taken from the 2009 Australian guidelines to reduce health risks from drinking alcohol)[12]



High concentrations of alcohol in blood may potentially affect any tissue and organ in the body, altering its function. The effect may be acute or chronic. Evidence of the health impact of binge drinking is more recent and often presents methodological limitations (due to the heterogeneity in estimation methods or the failure to control for potential confounders, including the participant´s own average alcohol consumption). These limitations explain why only a small number of meta-analyses include more than a handful of studies on the topic. Still, those meta-analyses identified strong associations between binge drinking and different health negative effects as we summarized below.

1. Binge drinking and cardiovascular disease

Although there is consistent evidence showing that low amounts of alcohol may be associated to a lower risk for coronary disease, binge drinking is clearly associated to an increase in cardiovascular risk.

Most of this evidence comes from Eastern European countries, especially Russia, where a sort of a natural experiment took place. All-cause, and specifically cardiovascular,

mortality varied greatly during the 80s and 90s. During the 80s life expectancy increased with Gorbachov´s government alcohol prevention campaigns; however, it fell abruptly during the first half of the 90s with the collapse of the old Soviet Union. These fluctuations have been related to alcohol consumption, mainly with the large prevalence of binge drinking since the alcohol consumption per capita was no greater than in other European countries. Later on, new reductions in mortality have been associated to the implementation of policies successful in reducing binge drinking prevalence.[13] Despite being ecological observations, no other explanation to these variations has been proposed.

Binge drinking is associated to various changes in pathophysiological mechanisms that may lead to adverse effects on the cardiovascular system. Although not well known yet, available evidence suggests that these mechanisms are related to: 1) generation of oxidative vascular stress and changes in the endothelial function; 2) the rebound of the prothrombotic state secondary to the reversal of the inhibitory effect on the platelet aggregation; 3) adverse effects on the lipid profile, with elevation of the LDL cholesterol in the absence of an HDL increase; 4) also, although alcohol lowers blood pressure for the first 4 hours after consumption, pressure elevates significantly around 20-24 hours post-consumption; 5) finally, it affects electric signal conduction, increasing the risk for arrhythmias. [13-15]

One of the first reviews examining the importance of the alcohol consumption pattern in cardiovascular health was carried out by Britton and McKee based on 6 cohort and 3 case-control studies. Although the concept of binge drinking was more associated with alcohol poisoning and drunkenness and definitions varied greatly, the authors concluded that, overall, the risk of cardiovascular mortality doubled.[16]

Bagnardi and colleagues published another review focused on coronary disease. Based on 6 studies (4 cohort studies and 2 case-control studies) they concluded that binge drinking and sporadic "excessive" alcohol consumption modifies the favourable effect of alcohol over the risk for coronary disease. Their meta-analysis estimated a relative risk (RR) of 1.10 (95% CI: 1.03-1.17).[17]

Roerecke and Rehm carried out another review of 14 studies (10 cohort studies and 4 case-control studies) to evaluate the risk for ischemic cardiopathy. They defined binge drinking as the consumption of 5 standard drinks per session or intoxication, and considered drinkers with no binge drinking (low risk average drinkers) as the reference group. They estimated an RR of 1.45 (95% CI: 1.24-1.70).[18]

In a case-control multi-national study (52 countries), INTERHEART,[14] the intake of 6 or more standard drinks in the previous 48 hours was associated to a risk increase (OR) for myocardial infarction of 1.4 (1.1-1.9), which was significant among those 45 and older (OR=1.57; 95% CI 1.1-2.25) and reached an OR of 5.33 (95% CI: 1.55-18.3) for those over 65 years of age.

Another important effect of binge drinking on heart health are the disorders in electric signal conduction. Several longitudinal studies have observed that for both healthy individuals as well as for those with a history of cardiovascular disease, binge drinking increased the risk for arrhythmias such as atrial fibrillation. The size of the risks ranged from 1.13 to 1.29.[15] Several mechanisms involved in these effects are described. Alcoholic intoxications bring about an increase in activity of the sympathetic system with a 17% increase of the heart rate in healthy individuals after binge drinking episodes; the diuretic effect with elevated aldosterone and antidiuretic hormone levels may cause an electrolyte

variation contributing a pro-arrhythmic. Further, the cardiotoxic effect of acetaldehyde may endure during the entire period of intoxication.[19]

Finally, binge drinking is consistently associated with a greater risk of stroke and associated mortality, even after a comprehensive adjustment for confounding variables, and hypertension. Even acute effects related to consumption in the preceding 24 hours have been observed in the young as well as in middle-aged people.[15] This increased risk seems to be related to ischemic and hemorrhagic stroke. A potential mechanism involved may be the effect of acute alcohol consumption on arterial blood pressure, both systolic and diastolic, independently from the average alcohol consumption.[20] However, this explanation is somewhat controversial and other authors defend that the evidence pointing to alcohol-associated hypertension as the mechanism increasing the risk for stroke is not sufficient since this risk persists even after adjusting for arterial blood pressure levels.[21]

2. Binge drinking, neuropsychiatric effects, and developmental effects

Prenatal exposure to alcohol is the most common preventable cause of mental retardation. It also impacts negatively fetal and perinatal development in different ways. Disorders in the structural neuronal development and associated functions, including a reduction in brain volume, disorganization of the central nervous system and structural and functional anomalies in the corpus callosum, cerebellum, caudate nucleus, and hippocampus.[22,23] A wide range of cognitive and behavioral anomalies have been observed in people who suffered prenatal exposure to alcohol. These include a low intellectual coefficient, hyperactivity, behavioral and adaptative disorders, or deficits in motor function, language skills, attention span, executive function, or spatial vision. Prenatal exposure to alcohol may produce an even wider range of disorders, referred to as Fetal Alcohol Spectrum Disorders (FASD). No safe amount of alcohol during pregnancy has been determined, further, that amount could be influenced by maternal age, and genetic, SES, and dietary factors among others.[24]

Henderson and colleagues´ systematic review on the effects of binge drinking during pregnancy included 14 studies. The fact that all of them were riddled with substantial methodological limitations kept the authors from observing consistent significant effects on any of the variables of interest (miscarriage, premature birth, low birth weight and size, fetal alcohol syndrome). However, previous animal models support potential harm to the neurodevelopment which renders this drinking pattern strongly unadvisable, especially when the binge drinking is performed frequently and/or with large amounts of alcohol.[25]

Several animal models, studies on humans based on neuroimaging, neurophysiology, and neuropsychology have observed alterations in brain development and maturation linked to binge drinking likely to cause structural damage and cognitive problems related to learning and memory skills.[26] In the long term, these alterations likely lead to low academic achievement, increase predisposition to, and severity of, alcohol use disorders, and the adoption of high risk behaviors such as driving under the influence of alcohol. Also, these disorders would be more damaging during adolescence, due to the neurochemical immaturity, limbic neuroplasticity, and an incomplete development of the prefrontal cortex and the circuits responsible for judgement and inhibitory control. All this combined with the anxiety associated to hormonal changes, would favor impulsivity and the adoption

of different risk behavior, including the onset of consumption and abuse of alcohol and other substances which, in turn may aggravate the inhibitory control.[27-29] Not surprisingly, Spear and other authors show an association between the early onset of alcohol consumption and more frequent binge drinking and cognitive disorders.[30]

Binge drinking has been linked to deficits in verbal memory skills and executive functions, especially in regards to deficient inhibitory control, one of the key differences regarding consequences when compared to those of regular "excessive" consumption.[26] These disorders are similarly likely across sexes, [31] and could engender a lower academic achievement.[32] Similar effect was identified by Montgomery et al. among college students. [33] Though, the latter included a previous meta-analysis reporting no significant cognitive differences. Yet this lack of an association has been explained by methodological issues, both in the definition of "excess" consumption and in how the cognitive alterations are estimated in the included studies,[33] an issue also raised in reviews based on other populations groups.[34] Deficiencies associated to attention, memory, and executive functions associated to binge drinking are qualitatively similar to those observed in alcohol dependency, with a double alteration of, first, the executive control (voluntary actions) and an increase in automatic and emotional processes (impulsive behavior). Taking into account that there is an association between the early adoption of binge drinking and the development of alcohol dependency in adulthood, some authors propose the theory of a continuum between those two health issues.[30,35,36] Although not confirmed, two explanatory neurobiological mechanisms, among others, have been proposed; e.g., the presence of genetic polymorphisms[37] or comorbidities and shared familial and environmental factors.[32]

3. Binge drinking and intoxications, accidents and violence

One of the most obvious health effects of binge drinking is acute intoxication, the result of consuming massive amounts of alcohol which increase the concentration of blood alcohol. This concentration, by itself, already carries serious risks. These risks can even be life-threatening starting at 3 g of alcohol per liter of blood. Researching these effects, however, presents methodological difficulties leading many studies to underestimate these risks.[38,39]

The role of alcohol consumption in the incidence of injuries due to accidents or unintentional injuries is well known. Alcohol alters coordination, cognitive processing, and/or reaction time. These changes are particularly important at young ages, especially if caused from binge drinking which increases this type of risk up to 4 times compared to non-binge drinkers.[40,41] Driving under the influence of binge drinking increases the risk for car accidents and other unintentional injuries exponentially and proportionally to the blood alcohol level reached.[32]

Also, the risk is greater among low risk average drinkers who binge drink than among those with at-risk average consumption with a similar blood alcohol in the 6 hours before the injuries.[42]

Binge drinking is also associated to an increase in intentional injuries caused by violent attacks to others (including fist fights, gender violence, sexual abuse, and homicides) or self-inflicted (injuries or suicide), especially among the young.[32,43,44] Binge drinking may have been practiced by the victim and/or perpetrator, which adds complexity to any investigation.[45] Several studies report important differences in these associations by sex or edu-

cational level. In addition, the causality is not always clear, since alcohol may be consumed ahead of time with the purpose of experiencing disinhibition or lessen the expected pain, or once those episodes have already taken place. In fact, alcohol intoxication typical of binge drinking has been associated to depression and injuries due to external causes, and substantial labor disabilities as a result. [46]

Kuntsche et al. also report a relationship between binge drinking and unsafe sexual practices. [32] In fact, according to a meta-analysis[47] the risk for such practices increases by 5% per 0.1 g/L of blood alcohol. These findings are consistent with the relationship observed between binge drinking and other alcohol consumption patterns when having sexual intercourse without a condom between HIV serodiscordant individuals,[48] which strongly suggests a greater risk for sexually transmitted infections among binge drinkers.

Further, binge drinkers may cause other important social harms, both direct (e.g., noise, vandalism) and indirect ones (e.g., legal and health care costs, productivity loss) which end up as a substantial and costly economic burden. For instance, only the costs associated to the health care consumed by binge drinkers is estimated to be $168,000 million in the United States o £1,700 million in Great Britain.[49]

4. Binge drinking and other health effects

On top of the effects already discussed, several studies have confirmed an important relationship between binge drinking and other health effects. Pre-clinical studies associate exposure to high alcohol concentrations to important alterations in the microbiota and intestinal permeability, causing immunological and inflammatory disorder across the digestive system. These alterations would explain damage to the lipid metabolism and the toxic and inflammatory effects observed in the liver and pancreas. [49-51] Some of this damage may be greater among at-risk average drinkers than in binge drinkers, especially if the binging is sporadic.[38] Other damage, such as steatosis and liver damage seem to be more severe among at-risk average drinkers who are also binge drinkers.[49]

Whereas some studies have reported that individuals with a low risk average consumption show a reduction in risk for diabetes type 2, binge drinkers, in stark contrast, are 5 times as likely to be diabetic. These figures may be the result of a mechanism combining alterations of the glucose metabolism and poor dietary pattern, although this claim remains controversial given the scarcity of methodologically sound studies available.[38,52]

Binge drinking is also associated with damage to lung tissue and skeletal muscle (myopathy, rhabdomyolysis), secondary renal involvement,[49,51] and immune system damage (phagocite disorders, cytokine depletion) which increases vulnerability to infection. [38] Other studies suggest an association between binge drinking and oncogenic effect in mouth, esophagus, and liver, although available evidence come from animal models, o from observational studies with no adjustment for important potential confounders such as average alcohol consumption or smoking.[49]

Conclusions

We could define binge drinking as a pattern involving consuming large amounts of alcohol in a short period of time reserved exclusively for this activity (WHO).[1] However, there is no scientific consensus in the definition of binge drinking due to the great heterogeneity in the definition of a standard drink, as well as in the individual and contextual factors influencing the pathophysiological and social effects of this drinking pattern. Also, different thresholds or ways of classifying this alcohol consumption pattern may better predict each of the acute and chronic effects associated with it. This complicates establishing a scientific consensus around its definition and makes it necessary to combine different indicators to identify all the negative aspects of binge drinking.

The non-existence of a safe threshold for regular or occasional alcohol consumption is obvious. Further, any intense alcohol consumption, regardless of the set threshold, carries important risks, not only for the drinker´s health (acute and chronic effects) but also for the people around them. At the individual level, it has been shown that any binge drinking harmful effects are worsened as the amount of alcohol consumed in each binge episode increases. In addition, given the pathophysiological differences in alcohol metabolism, it is important to establish different thresholds by sex.

To actually identify binge drinkers and describe the health effects associated to this drinking pattern, it is not possible to set a unique threshold. Logically, the selected definition sets the prevalence of individuals included in this at-risk group, the stability of this indicator, and its comparability across countries and epidemiological information systems.

In addition, as reported in recent studies, the chosen threshold depends on the ability to establish causal associations and to estimate the different health impacts of binge drinking. A cut point set too low could underestimate the most severe and least frequent health effects. [4,5] In contrast, a cut point set too high (more specific) would better allow the identification of certain consequences but would leave out a portion of binge drinkers with a less extreme consumption and other type of consequences. That is, selecting a definition must take into consideration what the main objective of the estimate is. Another option, in this case, could be combining different definitions or thresholds with the goal of better capturing the acute and chronic effects of this consumption pattern.

Similarly, a simple dichotomous classification of binge drinking may hide important differences in the amounts of alcohol consumed. A substantial portion of binge drinkers amply exceed the set thresholds, even with more generous definitions.[9,10] For this reason, some authors have suggested defining binge drinking using categories, thus, bypassing the traditional dichotomous definition.[4]

Another possible approach would be to combine the dichotomous definition of this pattern with complementary indicators, such as the frequency of the episodes, number and type of the usually consumed drinks during binge drinking (intensity), or the average alcohol consumed regularly. This practice may improve the sensitivity and predictive power of this type of at-risk drinkers, an important task in the classification of at-risk drinkers at the population level.

The risks involved in binge drinking, even if practiced only sporadically (e.g., once a year), are well known.[7] Thus, maybe we should expand the temporal frame used as a

reference to classify binge drinkers to more than the previous 30 days. And in any case, the time frame should be taken into account when estimating and comparing the effects of this drinking pattern. Binge drinkers, who often report a low risk average alcohol consumption, make up an important risk group which we may miss if we do not analyze in detail all the characteristics that determine binge drinking and its associated effects.

Annex I.
Evidence selection methodology

1. Definition of binge drinking

Due to the great heterogeneity observed in the literature on the topic of binge drinking, we selected key research articles from different scientific fields and geographic environments. For this task, we considered the main national and international epidemiological information systems, as well as reviews and original research articles from research groups already known for quality research in the field of binge drinking.

Spain:

Health and Drug Surveys. [53-57]

Other studies based on nationally representative data on prevalence and characteristics of binge drinking.[10]

Europe:

BLOOMFIELD ET AL. 2013. *Alcohol survey measures for Europe: A literature review*.[58]
GMEL ET AL. 2011. Risky single-occasion drinking: bingeing is not bingeing.[42]
MOSKALEWICZ ET AL. 2016. Comparative monitoring of alcohol epidemiology across the EU.[59]
LABHART ET AL. 2018. *After how many drinks does someone experience acute consequences-determining thresholds for binge drinking.*[5]

United States

WECHSLER ET AL. 1994. Health & behavioural consequences of binge drinking in college.[60]
NIAAA 2004. NIAAA Council Approves Definition of Binge drinking.[2]
HINGSON ET AL. 2017. *Drinking Beyond the Binge Threshold; Predictors, Consequences, and Changes in U.S.*[4]
PEARSON ET AL. 2017. Questioning the validity of the 4+/5+ binge or heavy drinking criterion in college and clinical populations.[61]

Australia:

NHMRC 2009. Australian guidelines to reduce health risks from drinking alcohol.[12]

United Kingdom:

DoH 1995. Sensible Drinking Report.[3]
UK Chief Medical Officers 2016. Low Risk Drinking Guidelines.[62]

Global:

COURTNEY & POLICH 2009. Binge drinking in young adults; Data, definitions, and determinants.[63]
PARADA ET AL. 2011. Definición consumo intensivo de alcohol adolescente (Definition of binge drinking among adolescents).[64]
FURTWAENGLER & DE VISER 2013. Lack of international consensus in low-risk drinking guidelines.[65]
KALINOWSKI & HUMPHREYS 2016. Governmental standard drink definitions and low-risk alcohol consumption guidelines in 37 countries.[66]
ROLLAND ET AL. 2017. Comparison between the WHO and NIAAA criteria for binge drinking on drinking features and alcohol-related aftermaths.[7]

2. Consequences of the binge drinking pattern

To identify scientific evidence related to the health effects of this drinking pattern, we designed 2 search strategies with free terms and descriptors (MesH) including the most often used terms to define the consumption patterns binge drinking, and its impact on health (acute and chronic) or at the social level.

Results were limited to articles published in the past 5 years, classified as reviews (narrative, systematic, or meta-analysis). These search strategies were applied to 2 repositories of scientific literature (PubMed and Embase) with the last search run done in June 2019.

REPOSITORY/SEARCH TERMS	No References
PUBMED	
Search (((“heavy episodic drinking” OR “binge drinking” OR “heavy drinking”) OR binge drinking[MeSH])) AND “alcohol related disorders”[MeSH]) AND (review[Publication Type] OR literature review[Publication Type] OR review literature[Publication Type] OR systematic review[Publication Type] OR meta-analysis[Publication Type])) Sort by: PublicationDate Filters: published in the last 5 years	130
EMBASE	
(('binge drinking'/exp/mj OR 'alcohol intoxication'/exp/mj) AND [humans]/lim AND [review]/lim) AND (2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py)	56

We selected certain articles based on title and abstract for a total of 17 review articles after eliminated duplicates. However, there were few meta-analyses, with most of the reviews being narratives. We also observed that many of the reviews included studies selected for other works, or that they included studies with methodological issues.

For these reasons, we complemented this batch with cluster searches of other reviews identified during the review of articles and of articles considered to be key in the health effect of interest.

Annex II.
Definition of binge drinking: differences across surveys and countries

1. Health Surveys in Spain (ENSE; EESE) and Europe (EHIS)

To learn about the health status and behaviors of the Spanish population, several nationally representative surveys are performed on a regular basis. The Spanish National Health Survey (ENSE, for its Spanish abbreviation) is a 1987 study carried out by the Spanish Department of Health, Consumption, and Social Welfare in collaboration with the National Statistics Institute from 2003 on. It collects health information from a nationally representative sample of community-dwelling residents of Spain from any age group. Among other topics, data include questions on health determinants such as alcohol. [53]

In addition, from 2009 Spain also carries out, on an alternating bases with ENSE, the European Survey of Health in Spain (EESE, for its Spanish abbreviation) on population residing in Spain and 15 years of age or older. Among many other topics, this survey enquires about the determinants of health in a comparable manner with other European surveys.[56] This Spanish section of the European Health Interview Survey (EHIS), includes alcohol information. This survey´s definition of binge drinking does not differentiate by sex, having a common threshold for both (60g ethanol) and it does not standardize the duration of the alcohol drinking time period. The lack of information on the standard drink (SD) combined with the variability of the consumption patterns and the differing amount of alcohol in the different standard drinks (both inter as intra-country), seriously limits the comparability of the indicator.

In 2010, a group of experts tried to standardize the methodology between ENSE and EESE to maximize quality, comparability, and stability in indicators of alcohol consumption such as binge drinking. This effort included a definition of sex-specific binge drinking (6 and 5 SDs for men and women, equal to 60 and 50 g of pure ethanol, respectively) and a definition of binge episode duration (previous threshold of 2 hours is extended to 4-6 hours per episode). Since then, its definition has stayed the same in the following ENSEs (2011 and 2017) as in the EESEs (2014-2019). *Only* the categories of binge drinking frequency were modified in both surveys since 2014.

The following table 1 summarizes the main indicators collected on the last editions of these 3 surveys.

Table 1. Main indicators collected on the last editions of the Spanish surveys.

	ENSE, 2011	EESE, 2014	ENSE, 2017	EESE, 2019	EHIS
Study population	15 y.o. and over	15 y.o. and over	15 y.o. and over	15 y.o. and over	15 y.o. and over
Time period of reference	12 m	12 m	12 m	12 m	12 m
Standard drink (SD) per occasion	6 for men 5 for women	6 for men 5 for women	6 for men 5 for women	6 for men 5 for women	60 g ethanol
Differential threshold by sex	Yes	Yes	Yes	Yes	NO
Definition of "session"	Approximately 4-6h	Approximately 4-6h	Approximately 4-6h	Approximately 4-6h	…at a party, a meal, meeting with friends, home alone…
SD assessment	Participant and equivalency card aid	Participant and equivalency card aid	Participant and equivalency card aid	Participant and equivalency card aid	NO
Frequency of episodes	**5 categories:** • Daily/almost daily • Weekly • Monthly • < 1 time/m • Never	**9 categories:** • Daily/almost daily • 5 to 6 days/w • 3 to 4 days/w • 1 to 2 days/w • 2 to 3 days/m • 1 time/m • < 1 time/mo • None in past 12 m • Never	**9 categories:** • Daily/almost daily • 5 to 6 d/w • 3 to 4 d/w • 1 to 2 d/w • 2 to 3 d/m • 1 time/m • < 1 time/m • None in past 12 m • Never	**9 categories:** • Daily/almost daily • 5 to 6 d/w • 3 to 4 d/w • 1 to 2 d/w • 2 to 3 d/m • 1 time/m • < 1 time/m • None in past 12 m • Never	**9 categorías:** • Daily/almost daily • 5 to 6 d/w • 3 to 4 d/w • 1 to 2 d/w • 2 to 3 days/m • 1 time/m • < 1 time/m • None in past 12 m • Never

ENSE: Encuesta Nacional de Salud (National Health Survey); EESE: Encuesta Europea de Salud en España (European Health Survey in Spain); EHIS: European Health Interview Survey
y. o.: years old; h: hour/s; d: day/s; w: week; m: months; g: grams

2. Surveys specific to consumption of alcohol and other drugs in Spain (EDADES, ESTUDES)

Starting in 1995, the Spanish National Drug Plan has conducted the Home Survey on Consumption of Drugs and Alcohol in Spain (EDADES, for its Spanish abbreviation) targeting residents of the country between the ages of 15 and 64 years.[54] The same organism has been conducting another survey since 1994, National Survey on Drug Use in Secondary School (ESTUDES, for its Spanish abbreviation), directed to those between the ages of 14 and 18.[55]

Binge drinking started to be assessed as a drinking pattern in 2003 as part of the survey EDADES, and in 2006 as part of ESTUDES with some definition variations in the different waves of each survey as well as between the surveys or when compared to the health surveys summarized above (ENSE; EESE; EHIS).

The following tables describe key indicator variables capturing this consumption pattern in both surveys.

Table 2. Key indicators of binge drinking in the survey EDADES

	EDADES 1999-2001	EDADES 2003-2005-2007	EDADES 2009-2011	EDADES 2013	EDADES 2015	EDADES 2017
BINGE DRINKING	No	Yes	Yes	Yes	Yes	Yes
Study population	15-64 y.o.	15-64 y.o.	15-64 y.o.	15-64 y.o.	15-64 y.o.	15-64 y.o.
Time period of reference	-	Previous 30 d	Previous 30 d	Previous 30 d	Previous 30 d	Previous 30 d
No. of SDs per session	-	5	5/4	5/4	5/4	5/4
Differential thresholds by sex	-	No	Yes	Yes	Yes	Yes
Duration of session	-	Approximately 2h	Approximately 2h	Approximately 2h	Approximately 2h	Approximately 2h
Differentiated no. drinks high/low alcohol content	-	No	No	No	No	No
Frequency of episodes	-	Yes (no. of days)	Yes (no. of days)	Yes (no. of days)	Yes (no. of days)	Yes (no. of days)
Differentiation by day of consumption	-	No	No	No	No	No

y.o.: years old; h: hour/s; d: day/s; number: no

Table 3. Key indicator variables of binge drinking in the survey ESTUDES

	ESTUDES 1994-2004	ESTUDES 2006-2012	ESTUDES 2014	ESTUDES 2016	ESTUDES 2018
BINGE DRINKING	No	Yes	Yes	Yes	Yes
Study population	14-18 y.o.	14-18 y.o.	14-18 y.o.	14-18 y.o.	14-18 y.o.
Time period of reference	-	Previous 30 d	Previous 30 d	Previous 30 d	Previous 30 d
No. of SDs per occasion	-	5	5	5	5
Differential thresholds by sex	-	No	No	No	No
Duration of session	-	Approximately 2h	Approximately 2h	7 categories: • < 1 h • 1-2 h • 3-4 h • 5-6 h • 7-8 h • 9 h or more • Haven´t done it in previous 30 d	Approximately 2h
Differentiated no. drinks high/low alcohol content	-	No	**Type of drinks when binge drinking**	**Type of drinks when binge drinking**	No
Frequency of episodes	-	8 categories • 1 d • 2 d • 4-5 d • 6-9 d • 10-19 d • ≥20 d • None (0)	8 categories: • 1 d • 2 da • 4-5 d • 6-9 d • 10-19 d • ≥20 d • None (0)	8 categories: • 1-3 d • 4-9 d • 10-19 d • 20-29 d • 30 d • Have not consumed ≥5 units of alcohol on one occasion on the previous 30 d • Have not consumed alcoholic beverages on the previous 30 d • I have never consumed alcoholic beverages	8 categories • 1 d • 2 d • 4-5 d • 6-9 d • 10-19 d • ≥20 d • None (0)
Differentiation by day of consumption	-	No	No	No	No

y.o.: years old; h: hour/s; d: day/s;

3. Estimates used in European countries

The most common definition for binge drinking presents important differences in different European countries. These differences derive from the alcohol content referred to as an SD and from alcohol consumption particularities.

The following table summarizes the most relevant differences, according to SDs and their equivalency, duration of the binging episodes, frequency and the time period taken as the reference.[59,67]

Examples of national standard drink definitions used in European countries

COUNTRY	No. SD PER BINGE DRINKING SESSION (men/women)	CONVERSION (pure alcohol in g)	Length of BINGE DRINKING session	REFERENCE TIME PERIOD	FREQUENCY OF BINGE DRINKING EPISODES	1 SD (pure alcohol in g)
Germany	5	70	1 d	Previous **12 m** and previous **30 d**		14
Austria	3/2	60/40				20
Belgium	6	60	1 d	Previous **6 m**		10
Bulgaria	6			Previous **12 m** (< 1 session)		10-14
Croacia	6	60				10
Denmark	6/5	72/60				12
Slovenia	6/4	60/40				10
Finland	5	60				12
France	6	60	**"Drinking session"**			10
Greece	5		**"Drinking session"**	Previous **30 da**	1/3/10 times	10-16
Hungary	6 5/4	60		Previous **12 m**		10
Ireland			**"Drinking session"**	Previous **12 m**		10
Iceland	5	50-60				10-12
Italy	6	72	**"Drinking session" <2 h**	Previous **12 m**		12
Latvia	5	60	**1 d/ party** or **celebration**			12
Lithuania	6	60	**"Drinking session"**			12
Norway	6	72-84				12-14
Poland	Beer: >1.5L Wine: >0.6L Vodka: >180 ml	60				10
Portugal	5	50				10
United Kingdom	8/6	64/48	**1 d**	Previous w		8
Sweden	• Beer with high alcohol content (4 cans) • Beer with low alcohol content (6 cans) • Wine (1 bottle, 750 mL) • Distillates (5 shots; 250 mL)	48-75				12
Switzerland	8	80-96	**"Drinking session"**			10-12

h: hour/s; d: day/s; month/s; w:week/s

4. Additional proposed definitions

In the past few years, institutions and researchers from different countries all over the world have redesigned or enhanced the definitions for binge drinking from different perspectives. The following table summarizes the most interesting aspects worth underscoring according to consumption threshold, the time period taken as reference, duration or frequency of the binging episodes, their intensity, or the type of drinks consumed during binge drinking.

Table 4. Examples of standard drink definitions

BINGE DRINKING	**MMWR 2012** Vital signs: Binge drinking prevalence, frequency, and intensity among adults-United States, 2010 (CDC Behavioural Risk Factors Surveillance System) [68]	**NHMRC 2009** Australian guidelines to reduce health risks from drinking alcohol (NHMRC)[12]	**SOLER-VILA et al. 2014** Binge drinking in Spain, 2008-2010 (ENRICA, binge drinking estimates, generalizable to Spain)[10]	**UK Chief Medical Officers 2016**. UK Chief Medical Officers' Low Risk Drinking Guidelines [62]	**HINGSON et al. 2017** Drinking Beyond the Binge Threshold: Predictors, Consequences, and Changes in the U.S. (NESARC)[4]	**ROLLAND et al. 2017** Comparison WHO and NIAAA criteria & alcohol-related aftermaths[7]	**LABHART et al. 2018** Comparison of acute effects, according to different thresholds, in students [5]
Time period of reference	Previous **30 d**	–	Previous **30 d**	–	Previous **12 m**	Previous **60 d**	Previous **30 d**
Time length of the session	Not specified "***drinking session***"	Not specified "*time sequence during which blood alcohol does not drop back to* ***0***"	***"afternoon or evening"***	**3-6 h**	***"1 day"***	**<2 h**	***"1 night"***
Sex-specific estimates	**YES**	**NO**	**YES**	**NO**	**YES**	**YES**	**YES**
Standard drinks (SDs) per session (men/women)	**5/4**	**4**	**8/6**	"***no advice on No. of units***" (individual and contextual differences)	***5-9/10-14/***≥**15** ***4-7/8-11/***≥**12**	**5/4** vs. **60 g**	**5/4** (among others; optimum threshold)
Conversion to grams of pure alcohol	**70/56**	**40**	**80/60**	–	**70-135/160-238/**≥**270** **56-105/128-187/**≥**216**	**70/56**	**50/40**
Frequency of episodes	**YES** no. of episodes	–	**YES** ≥3/<3	–	**YES** Daily/1-4 per w/1-3 per m/1-11 per year	**YES** (AUDIT-C) 1 per w/1 per m	**YES** No. of episodes
Intensity of episodes (no. drinks per episode)	**YES**	–	**YES**	–	**NO**	**YES**	**YES**
Differentiation no. drinks high/ low alcohol content	**NO**	–	**YES**	–	**NO**	**NO**	**NO**
Differentiation by day of consumption	**NO**	–	**NO**	–	**NO**	**NO**	**NO**
Differentiation average/regular consumption	**YES**	–	**YES**	–	**NO**	**YES**	**YES**
Key aspects worth underscoring	**NIAAA Standard definition** Enhanced by the addition of pattern´s intensity and frequency	Establishes **more strict** national recommendations, **omitting sex differences**	Definition based on 2013 United Kingdom´s (**double the amount of alcohol recommended as daily average**)[3]	Establishes **more strict** national recommendations than the previous ones**, omitting sex differences** as well	Compares different thresholds or definitions, with **increasing risk** for several acute effects	Greater risk for several acute effects, **even for occasional binge drinkers** (12 months)	Sensitivity analyses definitions for different acute effects, **optimal threshold set at 40/50g**

h: hour/s; d: day/s; w: week/s; m: month/s; no.: number

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3. Type of alcoholic beverages and differential health effects

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Abbreviations

HDL	High Density Lipoprotein
IARC	International Agency for Research on Cancer
LDL	Low Density Lipoprotein
OR	Odds Ratio
RR	Relative Risk
SD	Standard drink

Executive summary

In general, there is no question that alcohol consumption is a health risk factor contributing to an important disease burden. However, some studies have suggested that low doses of alcohol may have a beneficial effect in certain pathologies such as ischemic heart disease and ischemic stroke. There is also the greatly popular belief that certain alcoholic beverages have an "additional" benefit on top of the already controversial protective effect of the "moderate" consumption of alcohol. This is the case, mostly, of fermented drinks: wine (particularly red wine) and beer. Both drinks happen to be important production and consumption products at the European level in general, and in Mediterranean countries, in particular.

The potentially beneficial components in those alcoholic beverages are mainly ethanol and the phenolic compounds or polyphenols. On one hand, ethanol increases High Density Lipoproteins (HDL) inhibiting platelet aggregation and reducing inflammation. On the other hand, polyphenols contribute to the lowering of arterial blood pressure, inhibiting the oxidation of Low Density Lipoproteins (LDL), improving endothelial function, inhibiting platelet aggregation and reducing inflammation. However, when speaking of benefits, one should consider the adverse effects of alcohol consumption and the fact that the concentration of polyphenols in alcoholic beverages is very small.

Thus, out of the total average consumption of polyphenols in the Spanish diet, only 8-9% come from wine and 2% come from beer. Further, these amounts can be obtained in a healthy manner through the consumption of oranges, apples, or bread.

In contrast to the potentially beneficial effects, it could be argued that drinks with high alcohol content ingested in similar amounts to those of low alcohol content, may have greater adverse effects regarding injuries.

With the aim of performing a substantive analysis of the differential health effects of the various types of alcoholic beverages, the work group performed a review of systematic reviews and/or meta-analyses published from the year 2000 on. Recommendations based on the scientific evidence are provided.

The reviewed articles presented many methodological limitations. Among these, we found different methods of independently estimating the contribution of the type of drinks, insufficient control of confounding factors, such as demographic and lifestyle variables, as well as of those related to the characteristics of the alcohol consumption pattern. Speaking of which, it is worth underscoring that studies tend to fail to adjust for type of consumption, i.e., regular vs. occasional, with meals vs. outside meals, and, crucially, whether binge drinking is practiced. The latter is especially important as it varies substantially according to the type of drinks consumed.

The selected articles essentially cover three disease groups: cancer, cardiometabolic and neurodegenerative diseases. The epidemiological evidence reviewed fails to support the protective differential effect of beer or wine on our cardiometabolic system or any other, despite containing substances potentially beneficial to our health. Thus, recommending the consumption of certain alcoholic beverages on the basis of their differential benefits is not supported by the currently available scientific evidence.

Introduction

In general, there is no doubt that alcohol consumption is a health risk factor contributing to an important disease burden. However, some studies have suggested that low doses of alcohol may have a beneficial effect in certain pathologies such as ischemic heart disease and ischemic stroke. There is also the greatly popular belief that certain alcoholic beverages have an "additional" benefit on top of the already controversial protective effect of the "moderate" consumption of alcohol. This is the case, mostly, of fermented drinks: wine (particularly red wine) and beer. Both drinks happen to be important production and consumption products at the European level in general, and in Mediterranean countries, in particular.

The term "the French Paradox" was already coined in 1992 to describe the low incidence of cardiovascular diseases among the French population despite their elevated values in several risk factors such as the high consumption of saturated fats. Although an explanation was developed based on the high wine consumption among the French,[1] the authors pointed out that the HDL blood levels were not any higher than in any neighboring populations and suggested that other mechanisms had to be involved in the biological plausibility of this association.[2] Other authors blamed this controversial association on the poor adjustment for relevant confounding factors, especially dietary ones, such as the vegetable and olive oil consumption of the French population.[3]

The debate on whether the health impact of alcohol consumption ranges from harmful to beneficial by type of alcoholic drink consumed, lives on.

1. Action mechanisms

The action mechanisms of alcoholic beverages related to potential beneficial effects are extraordinarily complex due to the great number of involved pathways. First, an increase in HDL cholesterol concentration, a reduction in the platelet and fibrinogen activity, and an increased sensitivity to insulin. [4] The components in alcoholic beverages involved in these effects are mainly ethanol and the phenolic compounds or polyphenols. Ethanol increases HDL cholesterol, inhibits platelet aggregation, and reduces inflammation. Polyphenols contribute to lowering arterial blood pressure, inhibit the oxidation of LDL cholesterol, improve endothelial function, inhibit platelet aggregation, and reduce inflammation.[5]

The more than 8,000 phenolic compounds known can be divided into two large groups: the flavonoids and the non-flavonoids, being resveratrol in the latter group. Among the biological properties of these substances, their antioxidant role would be responsible of a large part of the mechanisms described above.

Whereas the amount of ethanol depends on the alcohol content of a drink, the concentration of polyphenols varies by type of beverage. For instance, the concentration in red wine is 10-fold that of white wine or beer. Nevertheless, we need to emphasize that the amount of polyphenols in alcoholic beverages is very small. In fact, of the average consumption of polyphenols in the Spanish diet, only 8-9% come from wine and 2% from beer.[6] For instance, an orange or an apple deliver similar concentrations of polyphenols

than a similar amount of red wine and much more than beer and the average consumption of bread (100 g/day) doubles it. In contrast, wine is the largest dietary source of resveratrol (over 98%).[7] However, most of the potentially beneficial biological effects attributed to this compound have been observed in "in vitro" research and animal experiments, and more evidence based on humans is needed. This compound has received a lot of attention due to its anti-inflammatory effects which may be involved in a reduction in cancer development. Nevertheless, some authors question its efficacy, emphasizing that, in any case, those effects must be minimal as an effective dose derived from ingesting this compound could never reach a preventative effect. [8]

In opposition to the potentially beneficial effects, it has been argued that some alcoholic beverages could have greater adverse effects, mainly those associated to accidents and violence. Experimental studies show that high alcohol content beverages consumed on an empty stomach produce a rapid increase of blood alcohol levels, greater than the intake of similar amounts of other lower alcohol content drinks. Consequently, beverages with high alcohol content may are substantially more likely to lead to aggressive behaviors,[9] and, although the evidence is not conclusive, to increase the risk of injuries.[10]

2. Methodological problems to consider when studying the health effect by type of drinks

The apparent health benefits of certain types of alcoholic beverages such as wine or beer, compared to non-fermented drinks with high alcohol content, may be the result of a combination of different methodological problems. First, there might be issues with the definition used to estimate the independent contribution of each type of drink and; second, there might exist substantial residual confounding derived from the different distribution of life styles and other alcohol consumption patterns.

Assessment of type of drinks

There are numerous approaches when it comes to evaluating the contribution of type of drinks to health effects. On one hand, there are numerous studies including the quantification of pure alcohol ingested by drink type, expressed in grams or SDs. On the other hand, several works estimate type of drinks preference, classifying it with different cut points. If an individual exceeds a certain threshold of their total alcohol intake by consuming alcohol from one of the 3 main drinks, they are classified as having a preference for wine, beer, or liquor, as the case might be. These thresholds vary between 50% of the total intake,[11,12] 80%,[13] or 20% more than the next most consumed drink.[14] If no consumption level meets these thresholds, the individual is classified as having "no preference." Sometimes, preference is not based on the amount of specific consumption but qualitatively based on the individual´s self-reported drink of choice.[15,16] Also, similarly to research on health effects of average alcohol consumption, many studies include never drinkers together with ex drinkers as the reference category which makes comparing and interpreting results extremely complex.

Considering the large number of ways of assessing the independent contribution of the type of drinks, reviews summarizing the related evidence should differentiate the analyses according to the definition used. Unfortunately, this is rarely done.

Residual confounding

Another one of the main criticisms regarding the controversial beneficial effects of consuming certain type of alcoholic beverages, is the failure to adjust for potential confounders, i.e., variables that are likely to modify the observed relationship.

First, it is well known that wine and beer drinkers, in contrast to liquor drinkers, lead healthier lifestyles. They are less likely to be smokers, more likely to exercise and have a higher level of physical activity. Further, they enjoy a higher educational achievement and socioeconomic status (SES).[11]

Second, a crucial aspect not always followed or described in the Methods section, is the need for statistical adjustment for other characteristics of alcohol consumption, for instance, the total amount of alcohol ingested. Drinking patterns should also be taken into consideration. Hence, analyses should take into account whether consumption is regular vs. occasional, if it takes place during meals vs. outside meals, and most importantly, whether binge drinking is practiced.

According to population-based data on individuals over 15 years of age,[17] the preferred drink of Spaniards (preference defined as >80% of the total pure alcohol intake) is beer, closely followed by wine. However, those who favor beer are mostly middle-aged men and women or younger, whereas wine is the preferred drink among those over 64 year of age. Liquor is preferred by the youngest group. This underscores the importance of adjusting for the right variables, not always mentioned in the studies limitations, but nevertheless crucial for correct interpretation of results. Similarly to many other industrialized countries, most of the alcohol consumed during binge drinking episodes comes from beverages with high alcohol content.[18]

3. Type of alcoholic beverages and dietary recommendations

Another key element reinforcing the belief that certain types of alcoholic beverages are beneficial for our health is that its consumption is associated to the Mediterranean dietary pattern, a model of balanced nutrition recommended by most dietary guidelines. In fact, a consumption of 1-2 SDs/day improves the score, compared to never-drinkers, in most Mediterranean diet scales.[19]

Along these lines, some scales such as the Mediterranean Diet Adherence Screener (MEDAS), [20] include wine intake specifically (≥7 glasses/week). In the Mediterranean Diet Serving Score (MDSS), fermented beverages (wine or beer, 1-2 glasses/day)[21] are included as an important component of the dietary pattern. Moreover, a Mediterranean alcohol consumption pattern has been proposed. It would correspond to a "moderate" consumption of wine or other fermented drinks during meals (2 glasses for men, 1 for

women).[22] However, two studies evaluating the relationship between this alcohol consumption pattern and the Mediterranean diet pattern found just a weak association. One study, based on the cohort study ENRICA,[23] reported that only 15% of those following a Mediterranean dietary pattern also had a Mediterranean alcohol consumption pattern. In the cohort study SUN[24] dietary patterns were similar across consumers of different types of drinks. In addition, increasing even further the controversy regarding the definition of dietary patterns, studies evaluating Mediterranean diet scales claim that few of these instruments meet psychometric quality standards.[25]

In Europe, food-based nutritional guidelines referring to alcoholic beverages as part of the diet are scarce. Belgium, Bulgaria, Greece, Cyprus, and Luxemburg recommend fermented drinks low in alcohol content, i.e., wine and/or beer. However, in Malta´s guideline, wine and beer only appear in its infographics.[26] In Spain, the Spanish Agency of Food and Nutrition Safety (AESAN for its Spanish abbreviation), representing the position of the National Department of Health, does not recommend the consumption of alcoholic beverages.[27] However, the position of some scientific societies, such as the Spanish Society of Community Nutrition[28] or the Spanish Nutrition Foundation,[29] is one of tolerance reflected in their explicit nod to the consumption of fermented drinks by including them in their infographics.

Study objective

To evaluate systematic reviews and meta-analyses published from the year 2000 onward reporting quantitative results about the health effects of consuming different types of alcoholic beverages. To make recommendations based on this scientific evidence.

Review of the evidence

We examined the existing systematic reviews and meta-analyses reporting on the health effects associated to the consumption of different types of alcoholic beverages. We excluded those reviews or meta-analyses not reporting quantitative results by type of drinks, those analyzing complications of previously diagnosed diseases, or those reporting conflict of interests. The search strategy for these reviews is described in Annex 1.

1. Characteristics of the included articles

Table 1 describes the main results of the studies included in the review. Tables 2-4 summarize table 1 by using a more visual design to report associations. Of the 26 studies meeting our selection criteria, 21 were related to cancer, 3 dealt with cardiometabolic diseases, 2 with neurodegenerative diseases, and 1 with overall mortality (a simultaneous analysis along with cardiovascular diseases).

About half of the selected works had as main objective to analyze the association of their outcome with type of alcoholic beverages,[30-43] whereas for the other half, this association was secondary to the evaluation of the overall effect of alcohol consumption.[44-55]

Most of the studies analyzed the three main types of drinks, wine, beer, and liquor. Two of them only examined wine,[31,40] one looked at beer,[42] and another one assessed wine and beer but not liquor.[33] The most common definition of consumption for each drink was the measure of grams of alcohol per day, but adjustments for total alcohol intake or consumption patterns were usually missing. Adjustment for potential confounders varied a lot and, overall, how combined data analyses controlled for confounders was poorly explained.

2. Effect of alcoholic beverages on overall mortality

Wood et al.´s review of evidence[53] regarding all-cause mortality by type of drinks concluded that, for any type of drink, mortality risk was proportional to alcohol intake. However, these associations were stronger for beer and liquor than for wine drinkers.

3. Cardiometabolic diseases and type of alcoholic beverages

Two reviews[33,53] analyzed the effects of consuming different types of alcoholic beverages on cardiovascular diseases. Both reviews divided the diseases into two subtypes, which var-

ied slightly, making comparisons more difficult. Using meta-analysis of available evidence Di Castelnuovo *et al.*[33] observed that, compared to non-drinkers, wine drinkers presented a lower risk for coronary heart disease, cerebrovascular disease, non-fatal vascular events, and cardiovascular mortality. Further, beer drinkers had a lower risk for coronary heart disease and non-fatal vascular events. In contrast, the meta-analysis published by Wood *et al.*[53] reported a lower risk for myocardial infarction associated only to wine consumption. An increase in risk for strokes, cardiac failure, and other coronary diseases (except for myocardial infarction) was associated to alcohol consumptions of 100g/week or more, especially if derived from beer or liquor. Despite these variations, the differences observed in cardiovascular events by type of drinks consumed were not statistically significant.

Only one review[35] examined the relationship between the consumption of different types of alcoholic beverages and diabetes mellitus type 2. In the dose-response meta-analysis, a U-shape curve is reported for the three types of drinks, observing a maximum risk reduction with intake levels 20-30 g/day for wine or beer and 7-15 g/day for liquor. Of all the different alcoholic beverages, wine was associated to a greater reduction of risk in terms of magnitude. Compared to non-drinkers, wine drinkers consuming <10g/day but also those consuming >20g/day had significantly lower relative risk (RR), 0.86 and 0.83, respectively. But these exposure categories were not statistically significant for beer or liquor consumption.

4. Cancer and type of alcoholic beverages

Twenty-one systematic reviews and/or meta-analyses have assessed the relationship between different types of cancers and wine, beer, and/or liquor intake.[30-32,34,36-52] The article distribution by type of cancer examined goes as follows: oropharyngeal (1), stomach (1), pancreas (1), colorectal (2), lung (1), breast (3), endometrial (2), kidney (2), bladder (1), prostate (1), brain (1), skin (1), thyroid (1), and hematopoietic and lymphatic system (3).

Wine, beer, and liquor consumptions were strongly associated to a greater risk for **oropharyngeal cancer**, regardless of type of drinks.[39]

A systematic review[45] analyzed the relationship between different types of alcoholic beverages and **stomach cancer** based on 13 cohort studies. A greater risk for this cancer was observed among beer and liquor drinkers but not for wine drinkers.

Wang *et al.*[52] explored whether different levels of alcohol intake, by type of drinks, were related to **pancreatic cancer** risk. The authors also examined whether there were differences by sex. They only found a greater risk for this cancer associated with a high consumption of liquor for the overall sample and for men. No other association was found.

Two articles analyzed the association between **colorectal cancer** and the intake of different types of alcoholic beverages,[32,42] based on a combined analysis of cohort studies and one meta-analysis including cohort and case-control studies, respectively. Cho *et al.*[32] reported a greater risk for this cancer for consumption levels greater than 30g/day of wine or beer, but the association closely failed to reach statistical significance for liquor (RR=1.21; 95%CI=0.99-1.47). Differences among types of drinks were not statistically significant. Zhang *et al.*[42] only examined the relationship between this type of cancer and beer consumption and observed a statistically significant increased risk for an average intake of 2 or more drinks a day.

Another review[30] explored the relationship between **lung cancer** and alcohol consumption by type of drinks. Fully adjusted models (including controlling for smoking) showed that intakes of 1 or more SDs of beer or liquor a day were associated with a higher risk for this cancer (although not statistically significant), and no association with wine was observed. Compared to non-drinkers, drinking up to 1 SD of wine a day seemed to be associated to a reduced lung cancer risk.

Three meta-analyses describe the relationship between intakes of different types of alcoholic beverages and **breast cancer**, two in women[31,49] and one in men.[44] The studies on women observed a positive relationship between alcohol consumption and increased risk for breast cancer, independently of type of drinks (beer, wine, liquor). However, when considering the dose-response curves, one of the studies observed an association between wine consumption below 10g[31] a day with a lower risk for this cancer compared to female non-drinkers. In contrast, no significant associations were found in males.

Two meta-analyses assessed whether there was an association between **endometrial cancer** and wine, beer, or liquor consumption with somewhat similar results. Zhou *et al*.[43] reported no association between intake of these different alcoholic beverages and this cancer. The meta-analysis by Sun *et al.*[38] revealed no association with alcohol intake from wine or beer but authors observed a greater risk for this cancer in women who drank liquor compared to women who did not drink any alcohol.

The association between alcohol consumption and **kidney cancer** was studied by 2 meta-analyses,[37,41] and another one explored the relationship with **bladder cancer**.[50] Authors found an inverse association between kidney cancer and wine, beer, and liquor, i.e., individuals with higher alcohol consumption levels had a lower risk of developing it.[37] Furthermore, the meta-analysis examination of the dose-response showed that an increase of 5g of alcohol a day, either wine, beer, or liquor, was associated with a lower risk.[41] Similarly, a lower risk for bladder cancer was also observed for higher consumption of wine or beer but not liquor.[50]

Vartolomei *et al.*[40] analyzed moderate wine consumption and risk for **prostate cancer** and found not association for total wine intake vs. no intake. However, they observed an increased risk for white wine consumption and a reduced risk for red wine.

One meta-analysis[46] examined alcohol intake by type of drinks and **brain tumors** such as glioma or meningioma. Wine or beer consumption showed no association except for liquor intake which did show to increase risk for these tumors.

Gandini *et al.*[34] looked into the plausible relationship between **skin cancer**, melanoma especifically, and beer, wine, and liquor consumption. No association was observed between total alcohol intake or any of the types of drinks and this cancer.

A meta-analysis of 15 studies[47] examined the association between types of alcoholic beverages and **thyroid cancer**. No significant association was supported between this cancer and wine or beer. The relationship with liquor could not be evaluated because only one study provided relevant data.

Finally, regarding **cancers of the hematopoietic and lymphatic system**, 3 articles met our selection criteria.[36,48,51] Compared to non-drinkers, beer drinkers seemed to have a lower risk for non-Hodgkin´s lymphoma but no association was found for wine or liquor consumers.[51] The lack of relevant studies precluded us from evaluating similar associations with Hodgkin´s lymphoma. For multiple myeloma, wine drinkers presented a lower risk compared to abstemious individuals. Beer or liquor intake did not show any relation.

[36] Karalexi *et al.*[48] carried out a systematic review to investigate whether consumption of different types of alcoholic beverages during the preconception period, in the case of fathers, or during gestation, in the case of mothers, was related to the risk for leukemia in their children. A greater risk for acute lymphoblastic leukemia was reported among children of male beer or liquor drinkers during the preconception period. Also, wine consumption during pregnancy was associated to a greater risk for acute myeloid leukemia. No other associations were observed.

5. Neurodegenerative diseases and type of alcoholic beverages

One review[54] examining 6 articles evaluated the relationship between the consumption of different types of alcoholic beverages and the risk for dementia. An inverse association with wine was observed among current wine drinkers and among those who consumed up to 14 SDs/week. Meanwhile, beer drinkers with highest consumption had a greater risk than those reporting lower intake. However, given the few studies available (1-4 depending on the sub-analysis), no conclusions by type of drinks could be reached.

Another review[55] analyzed the relationship between alcohol consumption and risk for developing Parkinson´s disease. No statistically significant associations were detected by type of drinks once tobacco and coffee/caffeine consumption were taken into account.

Interpreting this review's results

The results of this "umbrella review" are heterogeneous regarding the differential effects of the different types of alcoholic beverages on health conditions. The large methodological differences in the assessment of alcohol intake, adjustment for confounding variables, and the contrast of the assessments among types of drinks make it very difficult to conclude whether their effect on health is distinct or not.

The only study included in the review describing the association between type of drinks and overall mortality[53] describes a non differentiated effect because, although beer and liquor seem to have a greater negative impact than wine, those differences are not statistically significant. Similarly, this study does not find statistically significant differences when it comes to diverse cardiovascular diseases, although, again, authors suggest that perhaps wine has the least damaging effect of all drinks. However, a previous meta-analysis by Di Castelnuovo et al.[33] focused on the effect of wine and beer consumption on cardiovascular morbidity/mortality showed a lower risk for cardiovascular morbidity/mortality among individuals who had ever drank wine or beer than non-drinkers. These results remained significant after excluding ex-drinkers and sporadic drinkers from the reference category and, also, after including combined alcohol consumption as a covariable (data not shown). The description of the confounding variables in the selected studies and their control in the statistical analysis are not specified in this work.

The only review focused on evaluating the impact of alcohol on diabetes[35] showed a lower risk associated to wine consumption compared to zero consumption, whereas no association was found for beer or liquor. This effect was observed for different categories classified by amount consumed, and it remained significant after stratifying by cohort follow-up time, adjusting for body mass index and consumption of other alcoholic beverages. Authors brought attention to two important limitations: 1) Selected studies included two groups in the reference category: abstemious and occasional drinkers. Further, whether ex drinkers were excluded from the reference category was not specified; 2) Publication bias was detected. Also, half of the studies included in the review were based on self-reported diabetes as the definition for inclusion.

As mentioned in the document titled "Low risk alcohol consumption thresholds," according to the International Agency for Research on Cancer (IARC), alcohol is a Group A carcinogenic for which there is no safe level of exposure.[56] Thus, the European code against cancer recommends abstaining from alcohol consumption as the best prevention, and if consumed, they recommend limiting its intake.[57] Existing evidence is consistent in terms of the causal association with oral cavity, pharyngeal, laryngeal, esophageal, liver, colorectal, and female breast cancers. However, evidence is vague or less consistent for other cancers, as described in this review. Table 3 shows the classification of the IARC evidence for the different types of cancer included in this research.

Even when the evidence for a causal association between alcohol and cancers is highly consistent (i.e., oropharyngeal, colorectal, and female breast), the selected reviews do not show a differential effect by type of alcoholic beverage, rather observing harmful effects for each of them. An exception would be the null association observed in colorectal cancer for a consumption of <30 g/day for each of the three alcoholic beverages. However, the lineal relationship described for this type of cancer follows a gradual growth rate and,

at low doses, the association is small in magnitude. Thus, it is not surprising to find no association at low doses, especially if the total alcohol consumption is stratified by type of drinks. In fact, IARC´s report states that it is possible that alcohol impact on this type of cancer may be observed only with consumptions >30 g/day. [56]

For stomach, pancreatic, lung, and prostate cancers, the evidence linking them to total alcohol consumption remains insufficient.

In our review, the only inverse effect observed (i.e., lower risk for drinkers vs. non-drinkers) was for very small wine intakes and lung cancer. No such association was found with low doses of beer or liquor, which actually increased the risk for lung cancer starting at the 1 SD level. [30] In the review, Chao reports the many limitations associated to the studies included, such as the difficulty of adjusting for tobacco consumption (most studies adjust for packs-year). Further, few studies adjust for dietary, occupational, and environmental factors. Also, most of the studies included ex-drinkers in the non-drinkers category.[30]

In order to eliminate the residual confounding derived from the imperfect adjustment for tobacco consumption, the review by García-Lavandeira et al.[58] focused exclusively on non-smoking population. This review was excluded from our review for not meeting the criteria of reporting the combined results of the studies. However, it is worth mentioning that it failed to show a significant effect for any of the types of drinks, although wine and beer seemed to have no association with lung cancer. In contrast, based on a combined analysis published after the closing of our umbrella review[59] the authors observed that, compared to non-drinkers, those consuming very small amounts of wine and liquors, but not beer, presented a lower risk for lung cancer. These associations remained significant in sub-analyses with only never smokers. Thus, the association of type of alcoholic beverages and lung cancer is not conclusive.

There are some types of cancer not associated to alcohol consumption such as kidney and bladder. Furthermore, there are some cancers where inverse associations have been reported, although in the absence of evidence of causal association, such as hematopoietic and lymphatic system cancer. In fact, these are the cancer types for which we have found inverse associations, i.e., total alcohol consumption, even when stratified by type of drinks, is associated to a lower likelihood of developing those cancers. However, differences across type of drinks were very slight or the results were heterogeneous. For instance, two reviews [37,41] on kidney cancer reported that individuals consuming any of the three types of drinks had lower cancer risk than non drinkers.

Another review, evaluating the association with cancer of the bladder, reported a protective effect of wine and beer; whereas there were direct associations between beer intake and risk of non-Hodgkin´s lymphoma and between wine consumption and myeloma.

IARC concludes that there is not enough evidence on the association between alcohol and endometrial, brain, or thyroid cancers. We failed to find associations with any of the different alcohol beverages, except for an increased risk for endometrial cancer and brain tumors among liquor drinkers. However, the alcohol variable was broadly categorized as "consumption vs. no consumption."

IARC´s report[56] emphasizes that out of the 7 cancer types for which there is research including data by type of alcoholic beverage (oropharyngeal, laryngeal, esophageal, colorectal, breast, and hematopoietic), none showed differential associations by type of drinks.

Finally, alcohol consumption is one of the modifiable risk factors for dementia. However, although some studies show that small intakes could be associated to a lower disease risk, the evidence remains controversial. Xu et al.´s review, which analyzed the association of type of drinks and alcohol intake categories, is supported by very few studies.[54]

Thus, the lower risk for dementia observed with small wine intakes, not observed with beer or liquor, should be treated with a degree of caution aside from the methodological issue of including ex-drinkers in the reference category. In addition, Zhang et al.´s review of the association between Parkinson´s and alcohol showed no results for the three types of alcoholic beverages.[55]

Conclusions

In spite of beer and wine including components potentially beneficial to our health, the epidemiological evidence reviewed here fails to lead to the conclusion that wine and beer have a differential effect on cardiometabolic or any other health risk.

Therefore, based on the scientific evidence currently available, it is never justified to recommend the intake of certain alcoholic beverages for the sake of their differential benefits.

The existing administrations and scientific societies are called to reach a consensus when it comes to making recommendations in this issue. Only a unified message will communicate an unambiguous and clear message to health professionals and the general population.

Table 1. Main characteristics and results of the studies included in the review

First Author (year)	Health problems	Study type	Number of studies	Number of participants	Type of drinks	Measurement alcohol consumption	Key results	Authors' conclusions
Overall mortality and cardiometabolic diseases								
Wood (2018)[53]	Overall Mortality; Fatal and non-fatal cases of: stroke, myocardial infarct, coronary disease (non infarct) and cardiac failure	Cohorts	83 (global). Not listed by type of drinks	351,342 wine drinkers; 227,469 beer drinkers; 171,770 liquor drinkers	Wine, beer, and liquors	g/w	Measure of association: HR (95% CI) When compared to those with minimal intakes, overall mortality risk increases linearly for beer and liquor consumption, whereas the risk increase for wine drinkers is more moderate. HR (95%CI) per 100 grams/week of alcohol: Stroke: wine 1.01 (0.95-1.07); beer 1.11 (1.06-1.16); liquor 1.22 (1.18-1.26). Myocardial infarction: wine 0.93 (0.88-0.98); beer 0.99 (0.97-1.02); liquor 1.12 (1.07-1.17). Coronary disease (non-infarct): wine 0.97 (0.92-1.03); beer 1.02 (0.99-1.04); liquor 1.15 (1.10-1.20). Cardiac failure: wine 0.98 (0.85-1.13); beer 1.13 (1.08-1.18); liquor 1.16 (1.07-1.25). For cardiovascular diseases, differences across types of drinks fail to reach statistical significance.	No specific conclusions by type of drinks
Di Castelnuovo (2002)[33]	Fatal and non-fatal cardiovascular diseases	Cases and controls; cohorts	13 beer, 11 wine	Wine 201,308; Beer 208,096	Wine and beer	Drinkers vs. non-drinkers and dose-response in ml/d	Measure of association: RR (95%CI) Wine: drinkers vs. non-drinkers: 0.68 (0.59-0.77). J-shape dose-response curve, with top protection at 150 ml/d. Beer: drinkers vs. non-drinkers: 0.78 (0.70-0.86). No dose-response trend, neither lineal nor quadratic.	Significant negative association between low or moderate wine consumption and vascular risk. A similar association with beer, though weaker, and no statistically significant dose-response relationship found.
Huang (2017) [35]	Diabetes type II	Cohorts	13	397,296	Wine, beer, and liquor	Grams of alcohol/day, classified into three groups: (0-10 g/d), (10-20 g/day) and (>20 g/d).	Measure of association: RR (95%CI), reference category=no consumption. Wine: (<10g/d): 0.86 (0.80-0.92), (10-20 g/d): 0.83 (0.76-0.91), (>20 g/d): 0.83 (0.76-0.91); Beer: (<10g/d): 0.95 (0.89-1.01); (10-20 g/d): 0.93 (0.87-1.00); (>20 g/d): 1.01 (0.88-1.16). Liquor: (<10g/d): 0.94 (0.84-1.05); (10-20 g/d): 0.95 (0.84-1.08); (>20 g/d): 1.24 (0.87-1.77). Dose-response for the three types of drinks: wine: top protection= 20-30g/d (risk reduction=20%); beer: top protection= 20-30g/d (risk reduction=9%); liquor: top protection= 7-15g/d (risk reduction=5%)	Wine was associated to a significant risk reduction for diabetes type II. Wine could be more useful for diabetes II prevention than beer or liquor.

First Author (year)	Health problems	Study type	Number of studies	Number of participants	Type of drinks	Measurement alcohol consumption	Key results	Authors' conclusions
Cancer								
Turati (2013)[39]	Oropharyngeal cancer	Cases and controls; cohorts	10 (wine); 8 (beer); 8 (liquor)	N/A	Wine, beer, and liquor	Drinks/d. Exclusive consumption of one type of drinks (wine, beer, or liquor). 3 categories: occasional or no consumption (reference category); moderate consumption (1-2 drinks/d); high consumption (≥4 drinks/d)	Measure of association: RR (95%CI) consumption vs no consumption: wine=2.12 (1.37-3.29); beer=2.43 (1.92-3.07); liquor=2.30 (1.78-2.98) high consumption vs. no consumption: wine=4.92 (2.80-8.65); beer=4.20 (1.43-12.38); liquor=5.20 (2.77-9.78)	Alcohol consumption associated to greater oropharyngeal cancer risk. No significant differences by type of drinks
Fang (2015)[45]	Stomach cancer	Cohorts	13 beer, 11 wine and 12 liquor	1,197,197	Wine, beer, and liquor	Drinkers vs. non-drinkers	Measure of association: RR (95%CI) Wine: drinkers vs. non-: 1.02 (0.77-1.34). Beer: drinkers vs. non-: 1.21 (1.02-1.43). Liquor: drinkers vs. non-: 1.22 (1.05-1.43).	Beer and liquor consumption were significantly associated to stomach cancer.

Wang (2016)[52]	Pancreatic cancer	Cohorts	19 (not identified by type of drinks)	4,211,129 (11,846 cases)	Wine, beer, and liquor	g/d	Measure of association: RR (95%CI) (reference category: no consumption)
							Men:
							beer: light consumption =1.06 (0.84-1.34); moderate consumption=1.14 (0.94-1.39); wine: light consumption =1.00 (0.85-1.18); moderate consumption =1.00 (0.84-1.18); liquor: light consumption=0.97 (0.73-1.28); moderate consumption=1.01 (0.84-1.18); high consumption=1.66 (1.24-2.23).
							Women:
							beer: light consumption=1.00 (0.76-1.30); moderate consumption=0.94 (0.56-1.57); wine: light consumption=1.00 (0.86-1.15); moderate consumption=0.95 (0.74-1.23); liquor: light consumption=1.06 (0.90-1.26); moderate consumption=1.08 (0.90-1.31); high consumption =1,46 (0.80-2.67).
							Total:
							beer: light consumption=0.98 (0.86-1.11); moderate consumption=1.05 (0.93-1.19); high consumption =1.08 (0.90-1.30);
							wine: light consumption=0.97 (0.87-1.07); moderate consumption=0.95 (0.85-1.07); high consumption =1.09 (0.79-1.49);
							liquor: light consumption=1.02 (0.90-1.16); moderate consumption=1.09 (0.99-1.19); high consumption =1.43 (1.17-1.74).
								High alcohol consumption, especially liquor, is associated to an increased risk for pancreatic cancer

First Author (year)	Health problems	Study type	Number of studies	Number of participants	Type of drinks	Measurement alcohol consumption	Key results	Authors' conclusions
Cho (2004)[32]	Colorectal cancer	Cohorts	8	489,979	Wine, beer, and liquor	g/d	Measure of association: RR (95%CI) Beer: compared to non-drinkers, intakes ranging from 1-29 g/d: 1.01 (0.89-1.13); intakes ≥30 g/d: 1.37 (1.00-1.87). Wine: compared to non-drinkers, intakes ranging 1-29 g/d: 0.97 (0.89-1.05); intake ≥30 g/d: 1.82 (1.28-2.59). Liquor: compared to non-drinkers, intakes ranging 1-29 grams/day: 0.98 (0.88-1.09); intake ≥30 g/d: 1.21 (0.99-1.47)	Conclusions do not report results regarding differences by type of drinks.
Zhang (2015)	Colorectal cancer	Cases and controls; cohorts	21 (beer)	C & C: 4,577 cases and 8,081 controls Cohorts: 6,105 cases out of 876,916 individuals	Beer	drinks/d	Measure of association: RR (95%CI) Some consumption vs. no consumption=1.20 (1.06-1.37); vs. no consumption or occasional consumption: 1.03 (0.95-1.11) for low consumption; 1.09 (0.91-1.31) for moderate consumption; 1.37 (1.26-1.49) for high consumption. Per 1-drink/day increment: 1.13 (1.06-1.21)	High beer consumption has been associated to a greater risk for colorectal cancer
Chao (2007)[30]	Lung cancer	Cases and controls; cohorts	14	468,466	Wine, beer, and liquor	Standard Drink (SD)	Measure of association: RR (95%CI) in fully adjusted models Beer: compared to non-drinkers, consumption <1 SD/d: 0.85 (0.67-1.08); ≥1 SD/d: 1.20 (0.90-1.58). Wine: compared to non-drinkers, consumption <1 SD/d: 0.72 (0.52-0.99); ≥1 SD/d: 0.80 (0.65-0.99). Liquor: compared to non-drinkers, consumption <1 SD/day: 0.89 (0.69-1.16); ≥1 SD/d: 1.20 (0.98-1.48).	High beer and liquor intakes are associated to a greater risk for lung cancer, whereas moderate wine consumption may be inversely related to said risk.
Chen (2016)[31]	Breast cancer	Cases and controls; cohorts	26	539,721 from cohort studies and 25,974 from case and control studies	Wine	g/d	Measure of association: RR (95%CI) All studies combined, comparing the highest intake category with the lowest (including non-drinkers): 1.36 (1.20-1.54). Cohort studies: 1.25 (1.07-1.46); case and control studies: 1.44 (1.19-1.73). In the dose-response curve, very small intakes (<10 g/day) seem to be associated to a small reduction in risk, compared to female non-drinkers.	High wine intakes increase the risk for breast cancer, whereas low doses seem associated to a small risk reduction.
Key (2006)[49]	Breast cancer	Cases and controls	30 (beer); 32 (wine); 31 (liquor)	77,724 cases and 1,030,675 controls (N/A by type of drinks)	Wine, beer, and liquor	Alcohol consumption vs. no alcohol consumption	Measure of association: OR (95%CI): consumption vs. no consumption: Beer=1.16 (1.04-1.29); Wine=1.14 (1.05-1.24); Liquor=1.14 (1.06-1.23)	Alcohol consumption is positively associated to breast cancer, with no difference by type of alcoholic beverages.

First Author (year)	Health problems	Study type	Number of studies	Number of participants	Type of drinks	Measurement alcohol consumption	Key results	Authors' conclusions
Cook (2015)[44]	Male breast cancer	Cases and controls, and cohorts	20	2,378/51,959	Wine, beer, and liquor	Consumption yes/no	Measure of association: OR (95%CI) Beer: compared to non-beer drinkers, drinkers: 0.95 (0.79-1.13). Wine: compared to non-drinkers, drinkers: 1.06 (0.89-1.26). Liquor: compared to non-drinkers, drinkers: 0.89 (0.75-1.05).	Conclusions do not report results regarding different types of drinks
Zhou (2017)[43]	Endometrial cancer	Cohorts	6 (beer, wine, and liquor)	Sub-studies types of drinks: 4,438 cases out of 612,849 individuals	Wine, beer, and liquor	g/d, categorized into 2 groups: <1 SD/d; >1 SD/d	Measure of association: RR (95%CI) Upper vs. lower consumption Beer=0.94 (0.72-1.22); Wine=1.10 (0.80-1.51); Liquor=1.04 (0.86-1.27); RR(95%CI) 1 drink-increase Beer=0.99 (0.97-1.01); Wine=1.00 (0.99-1.01); Liquor=1.00 (0.99-1.01)	No association between endometrial cancer and alcohol consumption. No differences by type of drinks.
Sun (2011)[38]	Endometrial cancer	Cases and controls, and cohorts	7	Sub-studies types of drinks: Cases and controls: 2,277 cases and 8,040 controls; cohorts: 771 cases out of 129,317 individuals	Wine, beer and liquor	Comparison alcohol consumption at least once vs. never	Measure of association: OR/RR (95%CI) for some consumption vs. no consumption: Beer=0.91 (0.75-1.11); Wine=1.07 (0.92-1.25); Liquor=1.22 (1.03-1.45)	Alcohol consumption is not related to endometrial cancer risk. No conclusions by type of drinks.
Song (2012)[37]	Renal cell cancer	Cohorts, cases and controls, and cohort pooled analysis	1 (beer), 1 (wine and liquor), 10 (beer, wine and liquor)	Sub-studies types of drinks: C & C: 7,834 cases and 17,245 controls; cohorts: 3,244 cases out of 1,252,431 individuals	Wine, beer, and liquor	g/d	Measure of association: RR combined (95%CI) (top vs. bottom category, no thresholds identified) Cases and controls: beer=0.81 (0.70-0.91); wine=0.75 (0.59-0.91); liquor=0.76 (0.66-0.87); Cohorts: beer=0.75 (0.55-0.95); wine=0.81 (0.65-0.97); liquor=0.87 (0.77-0.97)	Alcohol consumption reduces risk of renal cell cancer. Same results across types of drinks

First Author (year)	Health problems	Study type	Number of studies	Number of participants	Type of drinks	Measurement alcohol consumption	Key results	Authors' conclusions
Xu (2015)[41]	Renal cell cancer	Cohorts and cohort pooled analysis	3 (beer, wine and liquor)	Substudies types of drinks: 3,652 cases out of 1,360,229 individuals	Wine, beer, and liquor	g/d	Measure of association: RR (95%CI) (for 5g/day increased consumption) Beer=0.89 (0.85-0.93); wine=0.94 (0.90-0.99); liquor=0.96 (0.92-0.99) Sex-stratified: Men: Beer=0.87 (0.83-0.91); liquor=0.95 (0.92-0.99). No association with wine Women: Wine: 0.82 (0.73-0.91). No association with beer or liquor	There are differences in the association between renal cell cancer and alcohol consumption, by type of alcoholic drink and by sex.
Mao (2010)[50]	Bladder cancer	Cohorts and cases and controls (population- and hospital-based)	13 (beer); 13 (wine); 12 (liquor)	Substudies types of drinks: 74,303 individuals	Wine, beer, and liquor	g/d	Measure of association: OR (95%CI) for any consumption vs. no consumption: Beer=0.86 (0.76-0.96); Wine=0.85 (0.71-1.00); Liquor=1.01 (0.87-1.15) Excess risk per 10g/day increase in consumption: Beer= -5.7% (-1.8 to -9.4%); Wine= -3.3% (-0.9 to -5.7%)	Alcohol consumption in general has not been associated to bladder cancer but a risk reduction has been identified for beer and wine
Vartolomei (2018) [40]	Prostate cancer	Cases and controls, case-cohorts	14 (wine), 4 (white wine), 4 (red wine)	455,413	Wine	Moderate consumption (definition varies across studies)	Measure of association: RR (95%CI) Wine total (moderate consumption vs. no consumption): 0.98 (0.92-1.05); white wine: 1.26 (1.10-1.43); red wine: 0.88 (0.78-1.00)	Moderate wine intake was not associated to prostate cancer risk. However, white wine moderate consumption increased the risk whereas the red wine decreased it.
Galeone (2013) [46]	Brain tumors	Cases and controls and cohorts	6 wine, 10 beer, and 7 liquor	Number of participants not completely specified	Wine, beer, and liquor	Drinkers vs. Non-drinkers	Measure of association: RR (95%CI) Wine: drinkers vs. non-drinkers: 1.01 (0.70-1.48). Beer: drinkers vs. non-drinkers: 0.96 (0.82-1.12). Liquor: drinkers vs. non-drinkers: 1.20 (1.01-1.42).	In the conclusions, authors do to mention results by type of drinks
Gandini (2018) [34]	Melanoma	Cases and controls and cohorts	8 wine, 10 beer, 8 liquor	Wine and liquor: 82,188; beer: 133,053	Wine, beer, and liquor	g/d	Measure of association: RR (95%CI) Wine: Highest consumption category vs. the lowest (no thresholds specified): 1.22 (0.95-1.57). Beer: Highest consumption category vs. the lowest: 1.03 (0.81-1.29). Liquor: Highest consumption category vs. the lowest: 1.08 (0.91-1.28).	In the conclusions, authors do to mention results by type of drinks

First Author (year)	Health problems	Study type	Number of studies	Number of participants	Type of drinks	Measurement alcohol consumption	Key results	Authors' conclusions
Hong (2017)[47]	Thyroid cancer	Cases and controls, cohorts and cross-sectional	15 (wine), 15 (beer), 14 (wine and beer), 1 (liquor)	3,121,404	Wine, beer, and liquor	Not available	Measure of association: OR/RR (95%CI), comparing maximum vs. minimum intake Wine: 0.95 (0.76-1.19); beer: 0.63 (0.34-1.16); wine and beer: 0.90 (0.70-1.10); liquor: only 1 study, cannot evaluate.	Alcohol intake reduced the risk for thyroid cancer. No conclusions by type of drinks

Psaltopoulou (2018)[51]	No-Hodgkin and Hodgkin lymphomas and leukemia	Cohorts	5 (beer, wine, and liquor)	Sub-studies types of drinks: 848,672 individuals	Wine, beer, and liquor	Consumption current/any vs. no consumption	Measure of association: RR (95%CI): current/any vs no consumption:
							Non-Hodgkin lymphoma:
							beer=0.88 (0.81-0.95);
							wine=0.96 (0.90-1.12);
							liquor=0.90 (0.79-1.02)
							Subtypes of non-Hodgkin lymphoma: diffused large B-cell lymphoma: beer=0.82 (0.72-0.94); wine=0.95 (0.84-1.08); liquor=0.84 (0.74-0.95); lymphoma follicular: beer=0.88 (0.74-1.04); wine=1.06 (0.76-1.48); liquor=0.95 (0.79-1.14); chronic lymphocytic leukemia/small lymphocytic lymphoma: beer=0.90 (0.79-1.03); wine=0.91 (0.77-1.07); liquor=1.07 (0.86-1.32). Hodgkin lymphoma: only 1 study, not evaluable
								Authors observed lower risk of non-Hodgkin lymphoma among alcohol consumers. By type, beer seems to be associated to a lower risk than other drinks.

Psaltopoulou (2015)[36]	Multiple Myeloma	Cases and controls, and Cohorts	11 (beer, wine and liquor), 1 (beer and liquor)	Sub-studies types of drinks: C & C: 2,496 cases and 14,525 controls cohorts: 606 cases out of 366,555 individuals	Wine, beer, and liquor	g/d, consumption in 3 categories: light (<12.5g/d); moderate (12.5-50g/d); high (>50g/d)	Measure of association: RR (95%CI) (alcohol consumption vs. no consumption): Beer=0.88 (0.73-1.07); wine=0.77 (0.67-0.89); liquor=0.99 (0.77-1.26)	Alcohol consumption, particularly wine, in women was associated with lower risk for multiple myeloma.
Karalexi (2017) [48]	Leukemia (in offspring)	Cases and controls	Acute lymphoblastic leukemia: 9 (wine, beer, and liquor) acute myeloid leukemia: 6 (wine and beer), 5 (liquor)	Sub-studies types of drinks: 7,270 cases and 18,944 controls	Wine, beer, and liquor	Alcohol consumption vs. no consumption (during mother´s pregnancy or father´s preconception period)	Measure of association: OR (95%CI) any consumption vs none: Paternal consumption during preconception period: Acute lymphoblastic leukemia: Beer= 1.20 (1.01-1.42); Wine=0.94 (0.67-1.31); Liquor= 1.18 (1.00-1.40) Acute myeloid leukemia: no studies available Maternal consumption during pregnancy: Acute lymphoblastic leukemia: Beer= 0.97 (0.79-1.21); Wine=0.94 (0.76-1.16); Liquor= 1.12 (0.85-1.49) Acute myeloid leukemia: Beer=1.16 (0.84-1.60); Wine=1.59 (1.22-2.08); Liquor= 1.46 (0.78-2.75)	Alcohol consumption was associated to acute myeloid leukemia. No conclusions by type of drinks.

First Author (year)	Health problems	Study type	Number of studies	Number of participants	Type of drinks	Measurement alcohol consumption	Key results	Authors' conclusions
Neurodegenerative diseases								

Xu (2017) [54]	Dementia (all-cause dementia (ACD); Alzheimer (AD); vascular dementia (VD))	Cohorts and nested cases and controls	5 (beer, wine, and liquor), 1 (wine and liquor)	70,150 cases of ACD; 49,535 of AD; 49,535 of VD	Wine, beer, and liquor	Current consumption (yes/no)
						Low consumption (<7 drinks/w); low to moderate consumption (<14 drinks/w); moderate consumption (7-14 drinks/w); moderate to high consumption (>7 drinks/w); high consumption (>14 drinks/w)
							Measure of association: RR (95%CI) (all-cause dementia were grouped for analyses)
							Current drinkers vs. no consumption: wine=0.67 (0.48-0.94); beer=1.04 (0.78-1.40); liquor=1.16 (0.80-1.69)
							Consumption <14 SDs/w vs. no consumption: wine=0.58 (0.39-0.87); beer=1.59 (0.75-3.41); liquor=0.93 (0.74-1.18)
							Comparing highest consumption vs. lowest consumption:
							wine=1.01 (1.00-1.02);
							beer=1.84 (1.01-3.34);
							liquor=1.16 (0.73-1.84)
								Alcohol consumption ≤12.5g was associated to lower risk for dementia; whereas high consumption (≥23 drinks/w or ≥38g/d) was associated to higher risk. No conclusions by type of drinks.

Zhang (2014) [55]	Parkinson	Cases and controls and cohorts	8 (beer and liquor), 9 (wine)	Beer: 581,489 (4,090 cases); wine: 582,390 (4,582 cases); liquor: 581,084 (3,841 cases)	Wine, beer, and liquor	drinks/day	Measure of association: RR (95%CI) consumption vs. no consumption RR not adjusted for tobacco or caffeine: Wine= 0.92 (0.72-1.17); beer=0.66 (0.48-0.91); liquor=0.92 (0.75-1.13). RR adjusted for tobacco or caffeine: Wine= 0.98 (0.67-1.44); beer=0.77 (0.52-1.14); liquor=1.05 (0.76-1.44).	Alcohol consumption, especially beer, might reduce the risk for Parkinson

CI: Confidence Interval; g: grams; d: day; w: week; OR: Odds Ratio; RR: Relative Risk; HR: Hazard Ratios; SD: Standard Drink

Table 2. Synthesis of the associations observed in the studies reviewed. Overall mortality and cardiometabolic diseases

Health Problem	First Author (year)	Alcohol consumption measurement	Wine	Beer	Liquor
Overall mortality	Wood (2018)	g/w (only drinkers)	(0/+)	+	+
Cardiovascular dis.	Wood (2018)				
Stroke		g/w (only drinkers)	0	+	+
Myocardial Infarction		g/w (only drinkers)	-	0	+
Coronary dis.		g/w (only drinkers)	0	0	+
Cardiac failure		g/w (only drinkers)	0	+	+
Cardiovascular dis.	Di Castelnuovo (2002)	Consumption/no consumption	-	-	
Diabetes mellitus II	Huang (2017)	<10g/d	-	0	0
		10-20g/d	-	0	0
		>20g/d	-	0	0

0 (null effect); + (greater risk); - (lower risk); empty cells (type of drinks not evaluated);

g: grams; d: day; w: week

Table 3. Synthesis of the associations observed in the studies reviewed. Cancer

Health Problem	First Author (year)	Alcohol consumption measurement	Wine	Beer	Liquor	Effect and level of evidence (IARC)[56]
Oropharyngeal c.	Turati (2012)	consumption/no consumption	+	+	+	Consistent causal evidence
Stomach c.	Fang (2015)	consumption/no consumption	0	+	+	Insufficient causal evidence
Pancreatic c.	Wang (2016)	Light consumption	0	0	0	Insufficient causal evidence
		Moderate consumption	0	0	0	
		Heavy consumption	0	0	+	
Colorectal c.	Cho (2004)	<30g/d	0	0	0	Consistent causal evidence
		≥30g/d	+	+	0	
	Zhang (2015)	consumption/no consumption		+		
Lung c.	Chao (2007)	<1 SD/d	-	0	0	Insufficient causal evidence
		≥1 SD/d	0	+	+	
Female breast c.	Chen (2016)	Category with heavier/lower consumption	+			Consistent causal evidence
	Key (2006)	consumption/no consumption	+	+	+	
Male breast c.	Cook (2014)	consumption/no consumption	0	0	0	Insufficient causal evidence
Endometrial c.	Sun (2011)	consumption/no consumption	0	0	+	Insufficient causal evidence
	Zhou (2016)	Upper/lower category	0	0	0	
Kidney c.	Song (2012)	Upper/lower category	-	-	-	No association
	Xu (2015)	increase 5g/d	-	-	-	
Bladder c.	Mao (2010)	consumption/no consumption	-	-	0	No association
Prostate c.	Vartolomei (2018)	Moderate consumption	0			Insufficient causal evidence
Brain tumor	Galeone (2012)	consumption/no consumption	0	0	+	Insufficient causal evidence
Skin c.	Gandini (2018)	Upper/lower category	0	0	0	Insufficient causal evidence
Thyroid c.	Hong (2017)	Upper/lower category	0	0		Insufficient causal evidence
Hematopoietic and lymphatic						
Acute lymphoblastic leukemia (offspring)	Karalexi (2017)	consumption/no consumption	0	0	0	Reverse association (insufficient evidence)
Acute myeloid leukemia (offspring)	Karalexi (2017)	consumption/no consumption	+	0	0	Reverse association (insufficient evidence)
Non Hodgkin´s Lymphoma	Psaltopoulou (2018)	consumption/no consumption	0	-	0	Reverse association (insufficient evidence)
Myeloma	Psaltopoulou (2015)	consumption/no consumption	-	0	0	Insufficient causal evidence

0 (null effect); + (greater risk); - (lower risk); empty cells (type of drinks not evaluated)

Table 4. Synthesis of the associations observed in the studies reviewed. Neurodegenerative diseases

Health Problem	First Author (year)	Alcohol consumption measurement	Wine	Beer	Liquor
Dementia	Xu (2017)	Current consumption/no consumption	-	0	0
		Category with higher/lower consumption	+	+	0
Parkinson	Zhang (2014)	Consumption/no consumption (adjusted)	0	0	0

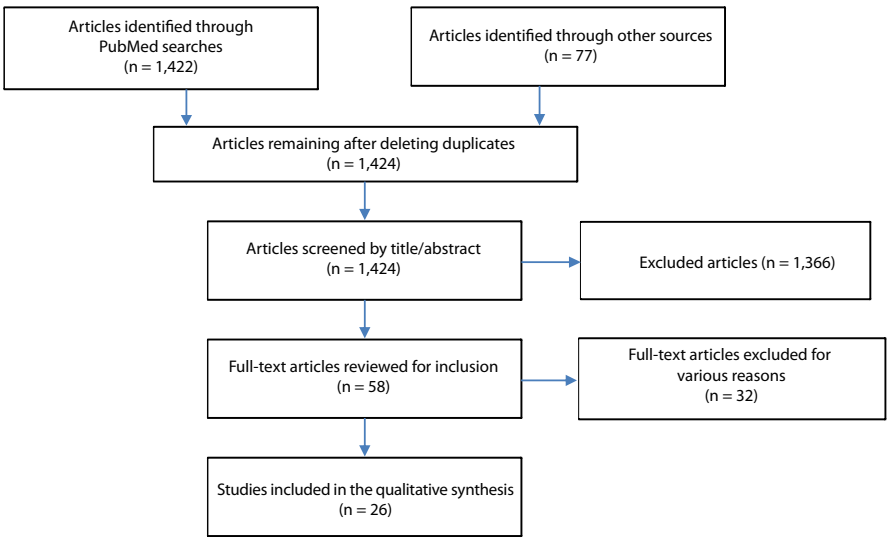
0 (null effect); + (greater risk); - (lower risk); empty cells (type of drinks not evaluated)

Annex I.
Methodology for evidence selection

We used the PubMed database to search for articles published from January 1st, 2000 until February 15th, 2019 using the following search strategy: ("alcohol"[All Fields] OR "alcoholic beverage"[All Fields] OR "wine"[All Fields] OR "beer"[All Fields] OR "spirits" [All Fields] OR "liquor"[All Fields]) AND ("adverse effects"[All Fields]OR "cardiovascular diseases"[All Fields] OR "stroke"[All Fields] OR "myocardial infarction"[All Fields] OR "coronary disease"[All Fields] OR "diabetes"[All Fields] OR "cancer"[All Fields] OR "obesity"[All Fields] OR "overweight"[All Fields]) AND (("systematic review"[All Fields] OR "meta-analysis"[All Fields]) AND ("2000/01/01"[PDAT]: "2019/02/15"[PDAT]) AND "humans"[MeSH Terms]). We also reviewed the reference lists of the articles selected to identify potentially relevant reviews or meta-analyses. Article selection and the following data extraction from each of them were performed by one reviewer and these tasks were reviewed by a second one. The information extracted from each of the articles is shown in **Table 1.**

Figure 1 presents the Flow diagram with the identified articles at the beginning and the articles dropped in each of phase of the selection process. We first identified 1,424 systematic reviews and meta-analysis based on title and summary. Of these, only 58 articles made it to the full text review. Twelve articles were excluded because they were neither systematic review nor meta-analysis, another 12 were excluded because the results were not presented by type of drinks in tables or figures, 3 were dropped for analyzing effects on biomarkers, 1 due to not collecting information on alcohol, another one because the information was already included in another selected article, and 3 for reporting conflicts of interests. Twenty-six studies were included in the final qualitative synthesis shown in **Table 1.**

Figure 1. Flow diagram describing the main stages of the selection process for the systematic review



Source: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097

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The objective of this document is to update the thresholds of alcohol consumption considered low risk, with the goal of reducing health problems, injuries, damages to third-parties, and socio-economic negative consequences derived from alcohol. Also it provide updates on alcohol-related damage to health professionals, according to levels and patterns of consumption. And provide evidence-based data on the differential potential health effects of alcohol by type of drinks.

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