Alcohol, Drinking Pattern, and Chronic Disease

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Alcohol is an addictive substance consumed worldwide, especially in European countries. Recommendations on alcohol consumption are controversial. On one hand, many nonrandomized studies defend that moderate consumption has a beneficial cardiovascular effect or a lower risk of all-cause mortality. On the other hand, alcohol is associated with an increased risk of cancer, neurological diseases, or injuries, among others.

Keywords: alcohol ; Mediterranean alcohol drinking pattern ; drinking pattern

1. Introduction

Alcohol consumption represents an important global health problem and a priority for public health. The Sustainable Development Goals explicitly target the goal to strengthen the prevention and treatment of substance abuse including narcotic drug abuse and harmful use of alcohol [1]. Harmful alcohol use is ranked as the seventh global leading risk factor for death and disability [2]. Annually, three million deaths are attributed to alcohol, together with wider social harms that also extend beyond the drinker including intimate-partner violence (with a heavy burden on women), exacerbation of poverty, traffic injuries, and other effects [3].

Alcohol-related health problems are particularly severe in Europe. Europeans are the heaviest drinkers in the world, with an average intake of pure alcohol >25 g/d among adults, and a prevalence of current drinkers (in the last 12 months) of 72% (61.4% among women and 83.3% among men) [4][5]. The prevalence of heavy episodic drinking (≥60 g on ≥1 occasion during the past 30 days) was 30.4% in Europe. An estimate of 291,100 deaths in 2016 were attributed to alcohol consumption in Europe (5.5% of European deaths, 12% of premature mortality in men, and 2% in women) [5]. Alcohol represents the third leading factor for death and disability in Europe, responsible for €125 billion in costs per year [6].

The burden of disease associated with alcohol consumption is usually assumed to result from an imbalance between beneficial and harmful effects. Nonrandomized epidemiologic studies have attributed some benefits to moderate alcohol consumption on ischemic heart disease, diabetes, or ischemic stroke, whereas they found detrimental effects on injury, suicide, several types of cancer, liver disease, mental disorders, and communicable diseases [2]. Considering the net balance, simple and generalized messages have been issued such as the safe level of alcohol intake should be zero [3][7][8][9][10][11] and “no level of alcohol consumption improves health” [7].

Absolute average alcohol intake does not seem to fully explain the shape of the dose–response relationship observed between alcohol intake and cardiovascular disease (CVD). Some aspects of the drinking pattern might act as effect modifiers including heavy episodic intake (binge drinking), beverage preference, consumption with or without meals, and distribution throughout the week [12][13][14][15][16][17][18][19][20][21]. Large cohorts concluded that ‘healthy’ patterns of moderate drinking reduce CVD [12][13][22][23][24][25][26][27][28][29][30], diabetes [31], and even all-cause mortality [32][33][34][35][36][37][38], particularly in subjects ≥50 years [26][29][39][40]. However, these cohorts included highly selected middle-to-high class subjects, highly educated subjects, or only health professionals. They also reported J-shaped associations for all-cause mortality. These effects might be dependent on the distribution of causes of death in the selected samples and on the distribution of levels of alcohol consumption in cohort participants, with few of them drinking high amounts or indulging in binge drinking [11]. This fact may compromise the strength of their potential causal inferences and generalizability [41][42][43][44][45][46].

In addition, studies using genetic instrumental variables or Mendelian randomization (MR) analyses have challenged that moderate alcohol consumption may reduce CVD or total mortality and support complete abstention as the healthiest option [47][48][49][50]. These analyses avoid the problems of self-selection for the drinking pattern, thus reducing confounding. They also provide a proxy of lifetime consumption and eliminate reverse causation. There are also limitations in MR analyses because, while MR analyses may contribute to identifying causal pathways, they cannot quantify the dose–response relationship between levels of alcohol consumption and mortality [51]. Several limitations

specific to the genetic underpinnings of Mendelian randomization analyses do not allow them to be fully equiparated to randomized trials [51][52][53]. Some assumptions of the MR analyses have been challenged when analogies for achieving causal inferences have been made between the effect of the genetic variant in a MR study and the intention-to-treat effect in a randomized controlled trial (RCT).

There are four weaknesses in such an analogy, as reported elsewhere in further detail [53]. First, the compared groups with different genetic variants in MR may not be balanced, as they are in large RCTs, because of linkage disequilibrium, population stratification, or other reasons. Second, the genetic variant is not always causal, but it might only be a misclassified version of an assigned treatment strategy and the important assumption of a strong homogeneity effect within each group required for the use of instrumental variables is usually not met in MR studies because it would be biologically implausible. Third, the definition of treatment “adherence” (that permits one to differentiate between intention-to-treat and per-protocol analyses) is unclear in MR and cannot be properly defined because the treatment strategies are not explicitly described. Fourth, and very importantly, “time zero” of follow-up (i.e., the inception instant in a trial) is usually not well defined in a MR analyses. In a RCT, “time zero” corresponds to the coincidence of four facts: the moment when the eligibility criteria are met, random allocation, the onset of the treatment strategy, and the starting time for counting the events of interest (outcomes). This does not occur in MR studies where a lag of several decades exists between the time of pseudo-randomization (“treatment”), the time of eligibility, and the onset of outcome recordings. These timing mismatches do not sustain a perfect analogy between a MR analyses and a RCT for causal inference. Thus, MR studies, despite contributing to identifying causal pathways, cannot replace large and well conducted RCTs [52][53].

Modeling studies such as the Global Burden of Disease (GDB) [2][4][5][6][54] are also currently invoked to support that total abstention is the healthiest alcohol dose [3][7][8]. Despite their utmost importance, these studies are in part based on some unfounded postulates [51]. They assume that true causal measures of effect are known for all relevant diseases and in all continents and countries as well as in the homeless, the less well-off strata, and other sectors of the population. They also assume that all relevant effect modifiers have been identified (to ensure extrapolation of previous estimates obtained in highly selected cohorts to external populations) and that accurate prevalence estimates are available for all countries. However, this is not the case [41][51][54][55][56]. These models are likely to be highly sensitive to the selection and precision of their inputs, which are not always explicitly disclosed. For example, tuberculosis importantly contributed to the estimated disease burden attributed to alcohol [2], but the GBD study included tuberculosis and not Hodgkin’s disease or other hematologic malignancies that previously showed inverse associations with alcohol [54][57]. They also ignored the effect of the drinking pattern (problematic drinking is considerably more important for tuberculosis than moderate alcohol intake) [58][59]. Additionally, an increased risk of colorectal cancer is only supported for >3 drinks/d [60], however, a purely linear dose–response shape was assumed by the GBD.

Several mechanistic studies have attempted to explain the pathways that may link alcohol intake to the pathogenesis of diseases. Both cell damage and protective mechanisms have been found depending on the dose of ethanol. High concentrations of alcohol trigger oxidative and cardiotoxic mechanisms in cells causing cardiomyopathy, arrhythmias, and heart failure [61][62]. Underlying mechanisms that associate alcohol consumption with the development of diabetes mellitus in mice have also been found [63]. On the other hand, low and even moderate concentrations of alcohol caused anti-fibrillatory effects in atria [61] as well as increased HDL cholesterol levels and improved heart energy metabolism profile [64]. Resveratrol has also been proposed as an anti-fibrillatory agent through the modulation of ROS and oxidative stress [65]. Moreover, the mechanisms involved in the association between alcohol and cancer have also been extensively studied, especially for breast cancer, where they highlighted the harmful effects of ethanol on breast cancer cells such as growth promotion and angiogenesis [66][67]. They also found that cells repeatedly treated with alcohol increased their ability to migrate and metastasize other tissues [67][68][69][70]. Despite the limitations presented by the in vitro and in vivo studies, they suggest possible mechanisms underlying the association between alcohol intake and the risk of chronic disease.

Alcohol was classified as a group 1 carcinogen 30 years ago, and it imposes a severe toll on cancer, being responsible for 4.1% of all new cases of cancers in 2020 [6]. Alcohol is causally linked to cancers of the oral cavity, pharynx, larynx, liver, esophagus (squamous cell carcinoma), breast, and colo-rectum [6][59][60][71]. Even moderate levels of consumption (about 1–2 drinks/d) have been found associated with higher risks including cancer of the breast [71]. Nevertheless, some important cohorts have reported inverse associations of moderate alcohol intake with total cancer. The European Prospective Investigation into Cancer and Nutrition (EPIC) found the lowest cancer risks for alcohol intake between 6 and 25 g/d. Even for ‘alcohol-related’ cancers, the lowest risk was found for 12–25 g/d [72]. Two large American cohorts reported the lowest risk of cancer death for participants with consumptions of 1–5 g/d, not for abstainers [37][73].

The drinking pattern may act as an effect modifier even for the relationship between alcohol intake and liver cirrhosis. In fact, a recent analysis found a 31% relative reduction in the risk of cirrhosis among drinkers with meals compared to drinkers outside meals, adjusting for the quantity consumed [74][75][76].

Specifically, wine consumption, particularly in Mediterranean countries, has been postulated as a key feature of the Mediterranean diet with strong cardio-protective properties [77][78] due to the abundance of polyphenols in red wine with postulated antioxidant or anti-inflammatory effects [79][80][81][82]. Researchers group also found an interaction between alcohol intake and the overall drinking pattern on mortality [14][16][19], concluding that a traditional Mediterranean alcohol drinking pattern (MADP) (i.e., a moderate consumption of red wine during meals, spread out throughout the week, and avoidance of binge-drinking) was associated with lower mortality compared to abstention or the departure from this MADP within constant levels of alcohol intake. A modification of the effect of the amount of alcohol intake on total mortality by the drinking patterns has been subsequently confirmed by recent large prospective studies conducted in the UK Biobank [75][76].

2. Alcohol Consumption and Chronic Diseases

Alcohol consumption is associated with a higher risk of acute diseases (infections, injuries, traffic accidents, violence, fetal alcohol disorders, among others) and variable effects on chronic diseases (diabetes mellitus, digestive diseases, cancers, CVD). The harmful effects of alcohol are largely influenced by the total amount of ethanol ingested, the drinking pattern, and the specific type of alcoholic beverage consumed [12][13][14][15][16][17][18][20][21]. This is even more important when it comes to chronic alcohol consumption (**Table 1**). Several studies have associated repeated exposures to large amounts of ethanol in the blood with increased oxidative stress. This effect is likely to occur because during alcohol metabolism, reactive oxygen species (ROS) and nitrogen species (RNS) are produced, which cause oxidative stress, cell damage, inflammation, and DNA oxidation, leading to mutations. It also has the potential to decrease antioxidant activity and can lead to chronic diseases such as diabetes, organ inflammation, cardiovascular problems, or cancer [83][84][85].

Table 1. Alcohol consumption and chronic diseases.

Protective Effects	Negative Effects
Alcohol and CVD	
Drinking pattern: low-moderate alcohol (♀ ≤7drinks/week, ♂ ≤14 drinks/week) + with meals + avoid binge drinking	**Chronic alcohol consumption, heavy drinking**
Effects on blood pressure, atrial fibrillation, or strokes	**High blood pressure, cardiomyopathy, coronary heart disease**
Articles: [12][13][16][17][21][22][23][24][25][26][27][28][29][30][39][40][85]	**Articles:** [47][48][49][50][86][87][88]
Alcohol and Diabetes Mellitus	
Low-moderate alcohol consumption	**Chronic alcohol consumption, heavy drinking**
Reduced insulin resistance, HbA1c levels and CVD risk	**Disruption in glucose homeostasis, higher insulin resistance, less adherence to diabetes treatment**
Articles: [31][89][90]	**Articles:** [89][91][92]
Alcohol and Digestive diseases	
Low-moderate consumption	**Chronic alcohol consumption, heavy drinking**
-	**Hepatitis, chronic liver disease, cirrhosis, pancreatitis, gastritis**
Articles: [93]	**Articles:** [2][4][94][95][96][97][98][99][100]
Alcohol and Cancer	
Low (1–5 g/day), moderate (12–25 g/day)	**All alcohol consumption, especially heavy and chronic patterns**
Lowest risk of cancer (even alcohol related cancers)	**Higher risk of breast, oropharynx, larynx, larynx, esophagus, liver, colon and rectum cancers**
Articles: [37][73][74]	**Articles:** [2][4][6][59][60][71][72]

2.1. Alcohol and CVD

Several nonrandomized studies have defended a J-shaped curve for the association between alcohol consumption and cardiovascular disease, with protective effects attributed to moderate consumption [12][13][16][17][22][23][24][25][26][27][28][29][30]. They emphasized the modifying effect of a moderate or healthier drinking pattern, particularly in subjects over 50 years of age [12][13][14][15][16][17][18][19][20][21][26][29][39][40], on potential alcohol beneficial effects on blood pressure, atrial fibrillation, or stroke [13][16][17][101]. One explanation for these potential benefits may lie in the antioxidant properties of wine, although there is still a large research gap to be filled [80][81][82][102]. On the other hand, some studies have argued for a linear association of alcohol with CVD or mortality [86][87][88] and attributed methodological problems and biases to the effects of moderate consumption and advocated zero alcohol [47][48][49][50].

2.2. Alcohol and Diabetes

Low-moderate alcohol consumption has been associated with reduced insulin resistance and HbA1c levels in non-diabetic patients and lower cardiovascular risk in diabetics [31][89][90]. However, there are studies that have challenged this claim as their findings also showed that diabetic patients who consumed alcohol adhered less to their treatment [91][92]. However, it is true that they agreed that chronic heavy drinking causes a disruption in glucose homeostasis, increases insulin resistance, and thus the risk of diabetes [89][91].

2.3. Alcohol and Digestive Diseases

The harmful effect of alcohol on the liver is well-known, leading to diseases such as hepatitis, chronic liver disease, and cirrhosis. Ethanol is metabolized in the liver, generating oxidative compounds and the accumulation of fatty acids. Therefore, hepatitis C or alcoholic fatty liver disease are the result of chronic high alcohol consumption [2][4][94][95][96][97][98]. Furthermore, although the liver is the main organ affected, high alcohol consumption can lead to pancreatitis [94][99][100] or gastritis [98]. However, it is important to note that moderate patterns do not seem to be as associated with these diseases as high consumption [93].

2.4. Alcohol and Cancer

Cancer, like cardiovascular disease, is one of the leading causes of death in the world. Due to the oxidative compounds caused by alcohol metabolism, cells are more prone to mutations and therefore a direct link to cancer is assumed. Most organizations advocate zero alcohol consumption to prevent breast, oropharynx, larynx, larynx, esophagus, liver, colon, and rectum cancers [2][4][6][59][60][71][72]. However, similarly to previous diseases, cohort studies have found that low or moderate alcohol consumption is associated with a lower risk of cancer than the abstainer group [37][73][74].

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