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REVIEW

Effects of moderate beer consumption on health and disease: A consensus document

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Abstract A large evidence-based review on the effects of a moderate consumption of beer on human health has been conducted by an international panel of experts who reached a full consensus on the present document.

Low-moderate (up to 1 drink per day in women, up to 2 in men), non-bingeing beer consumption, reduces the risk of cardiovascular disease. This effect is similar to that of wine, at comparable alcohol amounts. Epidemiological studies suggest that moderate consumption of either beer or wine may confer greater cardiovascular protection than spirits. Although specific data on beer are not conclusive, observational studies seem to indicate that low-moderate alcohol consumption is associated with a reduced risk of developing neurodegenerative disease. There is no evidence that beer drinking is different from other types of alcoholic beverages in respect to risk for some cancers. Evidence consistently suggests a J-shaped relationship between alcohol consumption (including beer) and all-cause mortality, with lower risk for moderate alcohol consumers than for abstainers or heavy drinkers.

Unless they are at high risk for alcohol-related cancers or alcohol dependency, there is no reason to discourage healthy adults who are already regular light-moderate beer consumers from continuing.

Consumption of beer, at any dosage, is not recommended for children, adolescents, pregnant women, individuals at risk to develop alcoholism, those with cardiomyopathy, cardiac arrhythmias, depression, liver and pancreatic diseases, or anyone engaged in actions that require concentration, skill or coordination.

In conclusion, although heavy and excessive beer consumption exerts deleterious effects on the human body, with increased disease risks on many organs and is associated to significant social problems such as addiction, accidents, violence and crime, data reported in this document show evidence for no harm of moderate beer consumption for major chronic conditions and some benefit against cardiovascular disease.

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Introduction

The multiple effects of alcohol consumption on human health have received increasing attention from the scientific community internationally [1]. However, while the harms associated with high intake of alcohol are well known, the effects of moderate doses (up to 1 drink -equivalent to 12 g of ethanol- per day in women, up to 2 in men of all types of alcoholic beverages combined) are more complex to deal with, and are the subject of a lively debate [1]. Of particular interest is the issue of the possible different effects of diverse alcoholic beverages (wine, beer, spirits), in relation to their heterogeneous content of non-alcoholic components. In particular, the question remains on the specific role of moderate consumption of beer, by far the most widely consumed alcoholic beverage throughout the world.

An international consensus document

It appeared thus appropriate to conduct an evidence-based review on the effects of the consumption of moderate amounts of beer on human health and disease.

A selected international Panel of independent scientific experts was gathered to develop a consensus document on beer consumption and health. Panelists contributed to this consensus on their own responsibility, not reflecting the opinion nor following the guidelines of any scientific society or association. To start, each panelist prepared a first draft manuscript on a specific aspect of the review's topic. Articles were individually retrieved by each panelist until November 2015, by search in PUBMED (MEDLINE), EMBASE and Cochrane Library using at least one of the following terms: beer, wine, liquor, spirits, alcohol in combination with health, morbidity, survival, death, cardiovascular or cancer or neurological or liver disease, hypertension, diabetes, supplemented by references included in the retrieved articles, meta-analyses and reviews. Studies were excluded if they were not in English. SC and ADC also carefully went through the volume "Beer in health and disease" edited by Victor R. Preedy, Elsevier, 2009. In several cases, the specific effects of beer consumption could not be separated from that of other alcoholic beverages: in that case the effects of alcohol itself were briefly reported.

All manuscripts were then exchanged and discussed among all panelists by mail/telephone and finally submitted to two external anonymous reviewers (one in Europe and the other one in USA). On the basis of the reviewers' comments, a pre-final text was prepared. A one-day meeting of the Panel was then held in Rome, during which the full text was read, commented and, when agreed upon by the Panel, modified. The consensus document was finalized few days later and submitted again to both external reviewers. The Panel unanimously approved the very final version and decided to submit it for publication to a peer reviewed journal specialized in nutrition and chronic diseases.

The preparation of the manuscript (in particular the organization and costs of the Panel meeting) was supported in part by *Assobirra*, the Italian Association of the Beer and Malt Industries. This funding source had no involvement in either study design, or selection of the Panel members, or collection and interpretation of data, or the writing of the report nor in Panel's decision to submit the manuscript for publication.

What is beer?

Beer has been included in the human diet since at least 5000 BC and as a product of the fermentation of cereals containing sugars and a variety of important nutrients (Table 1). Beer consists over 90% water; it contains carbohydrates and alcohol whose metabolism in the human body follows the release of an amount of energy. The alcoholic content of different kinds of beer varies and it is frequently estimated to range approximately from 3.5 to 10% w/v. Moderate intake of alcohol is considered up to 1 drink (typically a can of beer, 330 mL, containing about 4% w/v alcohol) per day in women and up to 2 in men. Using the food composition table (FCT) from the United States Department of Agriculture (USDA) [2] a can of 330 mL of an average beer contains approximately 140 Kcal. In a diet of 2000 Kcal in a general population, the almost "hidden liquid calories" of 1 drink of beer cover 7% of the daily energy requirements. Results from epidemiological and experimental studies provide inadequate scientific evidence to assess whether beer intake at moderate levels (i.e. $<$500 mL/day) is associated with general or abdominal obesity [3]. However, the extensive consumption of beer (i.e. $>$60 g/day of ethanol) may increase the risk for a positive energy balance that could lead to abdominal or general obesity [4,5]. Thus consumers should be informed on their daily energy requirements as well as on the caloric content of their preferred beer.

A small part of the caloric content of beer could be attributed to the metabolism of the carbohydrates it contains. According to the USDA FCT, a can of 330 mL of an average beer includes approximately 12 g of carbohydrates that may cover only 2.4% (i.e. 48 Kcal) of the daily energy requirements in a diet of 2000 Kcal. In addition, the mean content of simple sugars is zero [2].

Beer also contains trace amounts of minerals such as calcium, iron, magnesium, phosphorus, potassium,

Table 1 Mean nutrient composition of regular beer (data from USDA, National Nutrient Database for Standard Reference, Release 27) [2].

Compound	Units	Mean content	
		(per liter)	(per standard drink)
Water	g	920	306.7
Energy	kcal	430	143.3
Protein	g	4.6	1.5
Total lipid (fat)	g	0	0
Carbohydrate, by difference	g	35.5	11.8
Fiber, total dietary	g	0	0
Sugars, total	g	0	0
Minerals			
Calcium, Ca	mg	40	13.3
Iron, Fe	mg	0.2	0.07
Magnesium, Mg	mg	60	20
Phosphorus, P	mg	140	46.7
Potassium, K	mg	270	90
Sodium, Na	mg	40	13.3
Zinc, Zn	mg	0.1	0.03
Copper, Cu	mg	0.05	0.02
Manganese, Mn	mg	0.08	0.03
Selenium, Se	μg	6	2
Fluoride, F	μg	442	147.3
Vitamins			
Vitamin C, total ascorbic acid	mg	0	0
Thiamin	mg	0.05	0.02
Riboflavin	mg	0.25	0.08
Niacin	mg	5.13	1.7
Pantothenic acid	mg	0.41	0.14
Vitamin B-6	mg	0.46	0.15
Folate, DFE	μg	60	20
Choline, total	mg	101	33.7
Vitamin B-12	μg	0.2	0.07
Vitamin A, RAE	μg	0	0
Vitamin E (alpha-tocopherol)	mg	0	0
Vitamin D	IU	0	0
Vitamin K (phylloquinone)	μg	0	0
Lipids			
Fatty acids, total saturated	g	0	0
Fatty acids, total monounsaturated	g	0	0
Fatty acids, total polyunsaturated	g	0	0
Cholesterol	mg	0	0
Amino acids			
Alanine	g	0.12	0.04
Aspartic acid	g	0.16	0.05
Glutamic acid	g	0.47	0.16
Glycine	g	0.13	0.04
Proline	g	0.35	0.12
Alcohol, ethyl	g	39	13
Phenolic composition			
Flavonoids			
Flavan-3-ols			
Catechin	mg	3.8	1.27
Epicatechin	mg	0.8	0.27
Gallocatechin	mg	0.7	0.23
Flavonols			
Kaempferol	mg	8.1	2.70
Myricetin	mg	0.2	0.07
Quercetin	mg	0.1	0.03
Proanthocyanidin			
Proanthocyanidin monomers	mg	6.3	2.10
Proanthocyanidin dimers	mg	8.5	2.83
Proanthocyanidin trimers	mg	1.5	0.50
Proanthocyanidin 4-6mers	mg	4	1.33

sodium, zinc, copper, manganese and selenium, fluoride and silicon [2]. A quantity of 2 cans of 330 mL of beer contain almost 300 μg of fluoride that could approximately cover 10% of the recommended dietary allowance (RDA) for adults (i.e. 3000–4000 μg per day) [6]. This fact should be studied in parallel with the American Dietetic Association's statement about the impact of fluoride on health [7].

Beer has also been indicated as a rich source of dietary silicon [8] which is important for the growth and development of bone and connective tissue. Clinical studies are however required on the association of beer intake with osteoporosis prevention.

In addition, as a product of the fermentation of cereals, beer includes B-complex vitamins. Most of them are present in small amounts; however, folate and choline content is relatively significant. In particular, 2 cans of 330 mL of a regular beer contain approximately 40 μg of folate and 70 mg of choline [2] that cover almost 10% of the RDA of these vitamins [6].

Beer also includes a range of polyphenols such as flavonoids and phenolic acids that contribute directly to several beer characteristics such as flavor, haze, body and fullness [9]. In a recent identification of richest dietary sources of polyphenols [10] using food composition data of the Phenol-Explorer database, regular and dark beer servings of 550 mL took the 57th and 66th ranking positions, respectively. The total polyphenolic content for the same portions was estimated to 22 mg for regular beer and 10 mg for dark beer. Data from recent studies indicate a favorable role of polyphenol-rich food and polyphenol intake on inflammation biomarkers and possibly on the prevention of inflammation-related disease [11–14].

The content of polyphenols in beer is also influenced by the genetic factors of its raw materials, by the environmental conditions in which they grow, and by technological brewing factors [15].

In conclusion, beer consumption is associated with the intake of "liquid calories" and of significant amounts of fluoride, folate, choline, polyphenols and silicon. Further studies on the associations and interactions of the intake of these nutrients through beer with health outcomes are required in a public health perspective.

Additional aspects related to the consumption of beer, its spread and its production are discussed in the Appendix.

Beer consumption and cardiovascular risk

Since the proposal of a "French paradox" in the early Nineties [16], the possibility that consuming alcohol in the form of wine might confer a protection against coronary artery disease above that expected from its alcohol content has been extensively investigated.

There is consistent epidemiological evidence of a significant inverse association between moderate alcohol consumption and cardiovascular risk, coronary heart disease (CHD), in particular. A large meta-analysis (based on 16 studies including almost 290,000 healthy adults) published in 2011 [17] confirmed the significant reduction of vascular risk associated with wine consumption, but also showed a J-shaped relationship between beer intake and cardiovascular risk (Fig. 1 and Table 2). Moreover, the comparison of studies which included a parallel, but separate evaluation of wine or beer consumption, indicated a comparable protecting effect of either beverage, at comparable alcohol doses, against cardiovascular risk. In particular, Fig. 2 shows two similar dose—response curves for wine and beer consumption in relation to fatal and not fatal ischemic heart disease. The two curves were overlapping, especially at light-moderate alcohol consumption and the maximal protection by either beverage was 33% at 25 g alcohol/day. In contrast, no statistically significant association with vascular events was apparent for the intake of spirits. This might be due to the much lower proportion of subjects consuming liquors than that consuming wine or beer and very different patterns of liquor consumption. However spirits are also a type of alcoholic drink with the highest alcohol concentration but the lowest polyphenolic concentration, suggesting that the polyphenolic constituents found in wine or beer could contribute to the beneficial effect of alcoholic beverages on vascular events [18—20].

The main message from that meta-analysis [17] is that drinking alcohol in moderation appears to be more important than the content of the bottle, at least when wine and beer are taken into consideration. Although non-alcoholic components may play an important role, it cannot be excluded that the protective effect on cardiovascular events of wine and beer drinking in moderation could be (mainly) due to ethanol itself.

A review published in 2012 concludes that the main protective effects on the cardiovascular system resulting from moderate wine or beer intake is mainly due to their common components, both alcohol and polyphenols [21]. Beneficial effects of the moderate intake of alcoholic beverages against atherosclerosis have been attributed to their antioxidant and anti-inflammatory effects, as well as to their actions on vascular function: part of these effects may be linked to polyphenols contained not only in wine but in beer too.

Nowadays, the question whether the beneficial effects of alcoholic beverages (mainly) depend on the alcoholic or non-alcoholic components of these beverages is still open.

Protection of CHD and other cardiovascular outcomes by moderate alcohol consumption should be linked to alcohol's action on well-known cardiovascular risk factors (diabetes mellitus, elevated blood levels of low-density lipoprotein (LDL) cholesterol and triglycerides, reduced high-density lipoprotein (HDL) cholesterol) and thrombosis/fibrinolysis processes. The plausible mechanisms to explain these protective effects against ischemic cardiovascular disease (CVD) include an increase in HDL cholesterol, a decrease in platelet aggregation, a reduction in the levels of fibrinogen and an increase in insulin sensitivity, which have all been attributed to the ethanol content [21—23]. Other studies have provided evidence that wine exhibits beneficial properties which are independent of the presence of alcohol, and should be attributed to their polyphenolic content [18,19].

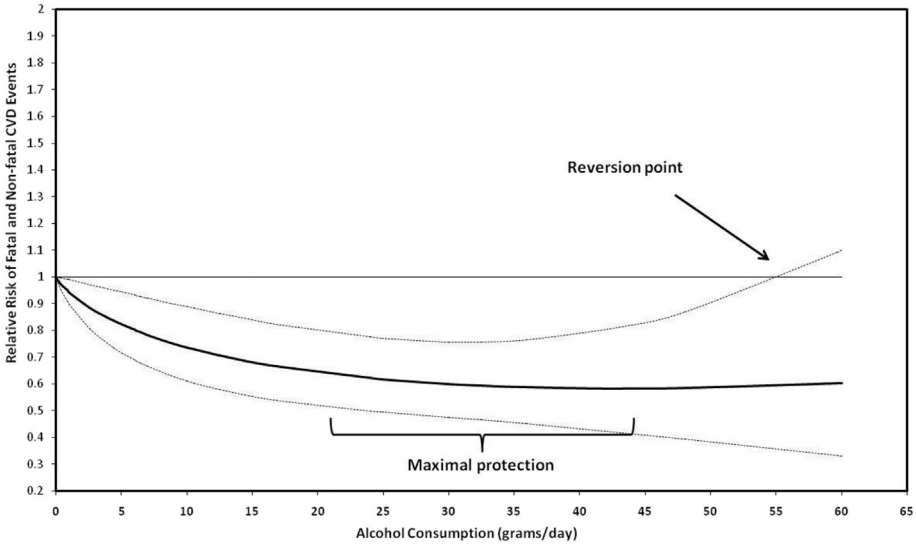

Figure 1 Beer intake in relation to CVD risk (modified from Costanzo et al. [17]).

Table 2 Summary of the studies on beer included in the meta-analysis on different alcoholic beverages in relation to cardiovascular events by Costanzo et al., 2011 [17].

Study	Type	Participants, *n*	Outcome	Categories of consumption	Results	Adjustment
Yano et al. N Engl J Med, 1977	Prospective	7705	Fatal non-fatal CHD	0 1–299 mL/day ≥300 mL/day	-1- 0.74 (0.57–0.97) 0.57 (0.42–0.77)	Age
Stampferet al. N Engl J Med, 1988	Prospective	87,526	Fatal non-fatal CHD	0 1–106 mL/day >106 mL/day	-1- 0.3 (0.2–0.8) 1 (0.6–1.6)	Age
Tavani et al. Epidemiol Biostat, 1996	Case–control	983	AMI	0 1 drink/day >1 drink/day	-1- 1 (0.7–1.3) 0.9 (0.6–1.4)	Age, education, residence, smoking, BMI, coffee, angina, diabetes, hypertension, hyperlipidemia, heart disease
Bobak et al. BMJ, 2000	Case–control	937	AMI	<0.5 L/week 0.5–3.9 L/week 4–8.9 L/week ≥9 L/week	-1- 0.65 (0.42–1) 0.34 (0.19–0.61) 0.54 (0.25–1.14)	Age, residence, smoking, education, WHR, diabetes, hyperlipidemia
Gronbaek et al. Ann Intern Med, 2000	Prospective	24,523	CHD mortality	0 1–7 drinks/week 8–21 drinks/week >21 drinks/week	-1- 0.78 (0.67–0.91) 0.63 (0.52–0.77) 0.78 (0.58–1.05)	Types of alcohol, age, sex, smoking, education, physical activity, BMI
Tavani et al. Eur J Epidemiol, 2001	Case–control	985	AMI	0 ≤1 drink/day >1 drink/day	-1- 0.6 (0.4–0.9) 0.4 (0.3–0.7)	Age, sex, education, BMI, cholesterol, smoking, coffee, physical activity, hyperlipidemia, diabetes, hypertension and family history of AMI.
Mukamal et al. N Engl J Med, 2003	Prospective	38,077	AMI	0 0.1–9.9 g/day 10–14.9 g/day 15–49.9 g/day >50 g/day	-1- 0.93 (0.83–1.04) 0.78 (0.61–1.01) 0.57 (0.37–0.89) 0.34 (0.12–0.92)	Age, smoking, BMI, diabetes, hypertension, hypercholesterolemia, family history of AMI; aspirin use, physical activity, energy intake; vitamin E, fat intake, and dietary fiber and for all other types of beverage
Mukamal et al. J Am Geriatr Soc, 2006	Prospective	4410	CHD	0 <1 drink/week 1–6 drinks/week ≥7 drinks/week	-1- 1.07 (0.80–1.43) 0.89 (0.60–1.31) 0.71 (0.43–1.19)	Age, sex, race, education, marital status, smoking, exercise intensity, depression score, aspirin use, BMI, diabetes and intake of other two beverage types
Harriss et al. Addiction, 2007	Prospective	38,200	CVD mortality (Male)	None 0–20 g/day 20–40 g/day >40 g/day	-1- 1.24 (0.9–1.71) 1.25 (0.78–2.02) 0.74 (0.37–1.48)	Age, country of birth, smoking, total daily energy and fruit intake.
Schroder et al. Nutr Metab Cardiovasc Dis, 2007	Case–control	1514	AMI	0 <20 g/day ≥20 g/day	-1- 0.17 (0.09–0.31) 0.22 (0.09–0.52)	Age and other alcoholic beverages
Streppel et al. J Epidemiol Community Health, 2009	Prospective	1373	CVD mortality	0 <20 g/day ≥20 g/day	-1- 0.91 (0.72–1.14) 1.26 (0.55–2.88)	Former drinking, energy intake smoking, intake of vegetables, fruit, fish, saturated and trans fatty acids, BMI, AMI, stroke, diabetes, cancer, socioeconomic status and total alcohol intake

Abbreviation: AMI, acute myocardial infarction; BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; IHD, ischemic heart disease; OC, oral contraceptive; WHR, waist to hip ratio.

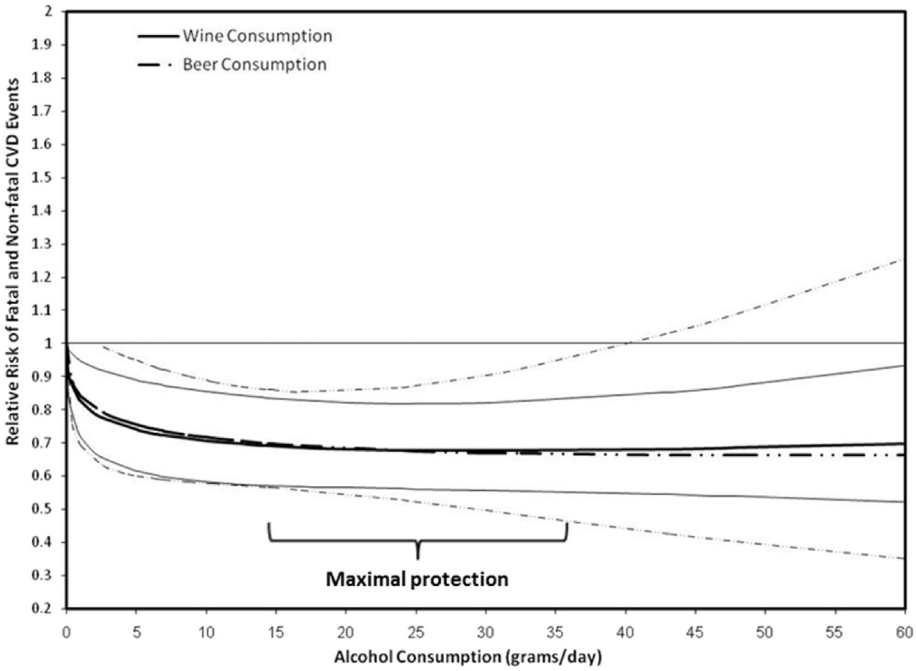

Figure 2 Comparison between curves from wine (solid lines) and beer (dotted lines) intake in relation to CVD risk (modified from Costanzo et al. [17]).

Likewise, the (poly)-phenolic contents in beer have shown different biological activities (shown in enzymatic assays or cell cultures) such as antioxidant, anti-carcinogenic, anti-inflammatory, estrogenic and even antiviral properties. Different profiles of *in vitro* biological activity have been described for these compounds which, combined together, could have a synergistic effect [21].

Regarding beer consumption, the effects of its alcoholic and non-alcoholic components on atherosclerotic biomarkers in high cardiovascular risk men have been evaluated in a randomized trial [20]. This experimental study concludes that the phenolic content of beer, similarly to what was previously observed with wine-derived polyphenols, reduces leukocyte adhesion molecules and inflammatory biomarkers, whereas alcohol mainly improves the lipid profile and reduces some plasma inflammatory biomarkers related to atherosclerosis.

The question of the effect of different alcoholic beverages on health is complicated by possible confounding as wine drinkers in Northern European countries, often have a more favorable overall cardiovascular risk profile, while in Mediterranean countries wine is more often drunk during meals [23]. Moreover the usual pattern of alcohol drinking may also be important: binge and heavy irregular drinking indeed nullifies the favorable effect of moderate alcohol (wine, beer) intake on CHD risk [24].

Binge drinking is the practice of consuming large quantities of alcohol in a single session, usually defined as five or more drinks at one time for a man, or four or more drinks at one time for a woman [1].

The evidence on the beneficial effects of moderate alcohol consumption (without any distinction between beer and wine) was also confirmed in patients who had experienced a first cardiovascular event. In a meta-analysis on CVD mortality, including 12,819 CVD patients, the overall relationship between cardiovascular mortality and alcohol intake was interpreted as a J-shaped curve, showing a protective effect (average 22% decrease) that was maximal in the range of 5–10 g/day [25].

Concerns exist whether findings of alcohol's protective effects on CVD may be biased by industry funding. In a recent study no evidence was found of possible funding effects for outcomes such as CVD mortality, incident coronary heart disease, coronary heart disease mortality, other than stroke [26] possibly because the effects of alcohol on this clinical outcome are more uncertain (see the next chapter) [26].

In conclusion, the main message for an adult general population can be summarized as follows:

- Epidemiologic studies indicate that consumption of low-moderate doses of beer are protective against cardiovascular risk in an adult healthy population [17]. Such a protective effect is comparable to that reported for moderate wine consumption but is not shared by spirits.
- Binge drinking of beer (or of other alcoholic beverages), even on limited occasions such as weekends, should be strongly discouraged [24].
- Heavy beer drinkers (as well as those exceeding the recommended intake of any alcoholic beverages) should be urged to cut and modify their consumption [22].
- Unless they are at high risk of alcohol-related cancers (see next chapter), there is no reason to discourage healthy adults who are already regular light-moderate beer (or other alcoholic beverages) consumers from continuing to follow the same pattern [17].

- Consumption of beer (and other alcoholic beverages), at any dosage, is not recommended for young people, pregnant women, those at risk of alcoholism, those with cardiomyopathy, cardiac arrhythmias, treated with selected drugs (antidepressants such as selective serotonin reuptake inhibitors) or liver or pancreatic diseases or during performing actions that require concentration, skill or coordination [22].

Although low-moderate, non-binging beer (alcohol) consumption – in the absence of contraindications and in the context of healthy eating and a healthy lifestyle – reduces the risk of CVD, we do not recommend that adult total life-long abstainers begin drinking for health reasons. This is because there is a risk that some of those who start to drink will consume more than the low-risk drinking amounts [27].

Beer consumption and stroke

As mentioned above, a large meta-analysis [17] indicates a comparable protecting effect of both wine and beer against cardiovascular risk (Figs. 1 and 2). However, a similar meta-analytic conclusion concerning stroke risk cannot be acquired, because of the lack of a sufficient number of epidemiologic studies on the topic.

In fact, very few studies provided prospective data on the association of beer intake and risk of stroke.

- In The Copenhagen City Heart Study [28] (13,329 men and women, aged ≥45, 16 years of follow-up, 833 first-ever strokes events), the Authors failed to observe any association between intake of beer and the risk of both ischemic or haemorrhagic stroke.
- In The Framingham Study [29] (5209 men and women, aged ≥30, 10 years of follow-up, 441 first-ever ischemic strokes) the Authors observed no effects for beer (hazard ratio (HR) 1.0; 95% Confidence Interval (CI): 0.8–1.4).
- In The Cardiovascular Health Study [30] (4410 men and women, ≥65 years, 9.2 years of follow-up, 434 cases of incident ischemic stroke), the Authors observed that 1–6 servings of beer per week, compared with abstention, were associated with lower risk of ischemic stroke (−61%; 95% CI: −16% to −81%), whereas a higher intake was associated with a non-statistically significant increase of risk (+65%; 95% CI: −0.2% to +128%).

As for ischemic cardiac disease, numerous mechanisms have also been suggested that would mediate the protective effect of alcohol on cerebrovascular events (i.e. increased levels of HDL cholesterol, decreased levels of LDL cholesterol, reduction in platelet aggregation, beneficial effects on inflammation) [22]. On the other hand, anti-atherogenic and anti-thrombotic effects and regulation of endothelial function (i.e. enhanced release of nitric oxide) were mainly ascribed to non-alcoholic components (polyphenols) of alcoholic beverages; such constituents being present not only in wine but also in beer [20].

In conclusion, the relationship between alcohol consumption and stroke is complex, in part reflecting the heterogeneity of this vascular disease. There is a J-shaped relationship between alcohol consumption and ischemic stroke, with lower risk for moderate alcohol consumers [31]. So far, existing data on beer are not conclusive, although some results indicate a positive role of drinking beer in moderation (1 drink/day) against ischemic stroke [30]. Heavy alcohol (and then beer) consumption increases the risk of stroke, both ischemic and hemorrhagic. Alcohol (beer) consumption should not be encouraged for those who do not already drink because of the harm associated with potential heavy use. Further research is needed to better assess whether moderate beer consumption has a beneficial effect for specific subtypes of ischemic and hemorrhagic stroke.

Beer consumption and cardiovascular disease prevention: possible physiological and biochemical pathways

Current evidence obtained from epidemiological studies has pointed out the protective effect of moderate drinking on the cardiovascular system, including CHD, ischemic stroke, peripheral arteriopathy and congestive heart failure. Positive effects have also been reported for moderate alcohol consumption on cellular aging damage, cognitive function and dementia [1]. However, the highest level of scientific evidence can only be obtained by randomized clinical trials. To date the few randomized studies performed have only focused on intermediate markers of cardiovascular risk. Studies on hard end-points as final variables are still lacking [1,22].

Effects of ethanol

Since beneficial or harmful effects are observed after the consumption of either wine or beer in a dose-dependent manner, these effects are most likely due to ethanol itself. Accordingly, lower risk of myocardial infarction in both sexes has been mainly related to the effects of moderate alcohol consumption on lipoproteins (HDL), coagulation (fibrinogen) and sensitivity to insulin.

Except in people with liver impairment, alcohol ingestion raises serum HDL-cholesterol levels. Inverse relations of HDL-cholesterol and CHD risk operate substantially via removal of lipid deposits in large blood vessels. HDL also binds with cholesterol in the tissues and may aid in preventing LDL cholesterol oxidation [22]. The net effect is a reduction in plaque building up in walls of large blood vessels, such as coronary arteries. Triglycerides may also play an independent role in the risk of CHD. A subset of heavy drinkers has a substantial increase in triglyceride levels, but this is infrequently seen in light to moderate drinkers.

Alcohol also inhibits several promoters of blood clotting, including platelet stickiness and fibrinogen levels. In addition, moderate alcohol consumption also affects the fibrinolytic system, increasing plasminogen activator

inhibitor activity and reducing plasminogen activator activity in the postprandial period (5 h after eating), a fact that might explain the reduction in the early morning risk of cardiovascular events observed in moderate drinkers who consume alcohol with dinner [21].

Finally, a meta-analysis of prospective observational studies has concluded that moderate alcohol consumption lowers the risk of type-2 diabetes [32]. In the same way, randomized clinical trials have also shown that moderate alcohol intake has beneficial effects on insulin concentrations and insulin sensitivity in non-diabetic patients, suggesting that moderate alcohol consumption decreases the risk of CVD and type-2 diabetes by improving insulin sensitivity [33].

Effects of polyphenols

As mentioned above, polyphenols and their metabolites can contribute to protect against CVD [18,19]. In an observational study within the PREDIMED (PREvención con DIeta MEDiterranea) trial, those participants who reported a high polyphenol intake showed a reduced risk of overall mortality, and also a lower incidence of CVD, compared to those with lower intakes [34]. In addition to alcohol, wine and beer contain polyphenols which could confer additional beneficial health properties compared to other types of alcoholic beverages. Polyphenols in wine [35–37] and beer [20] decrease blood pressure while increasing plasma nitric oxide concentration. Fig. 3 shows the changes in systolic and diastolic blood pressures after 4-week intervention with alcoholic beer, de-alcoholized beer and gin [20]. Interestingly, data suggest that only non-alcoholic, but not alcoholic beer intake, was associated with a decrease of blood pressure [20]. One can speculate that alcohol counteracts in some way the effects of polyphenols, at least in decreasing blood pressure. The inverse association between moderate alcohol intake and low diabetes risk was most apparent in wine and beer drinkers as compared to those who reported spirit intake. Accordingly, in a randomized clinical trial that examined the effects of three interventions (red wine, de-alcoholized red wine and gin), both red wine and de-alcoholized wine decreased HOMA-insulin resistance index, a measurement of insulin sensitivity, suggesting that polyphenols contained in wine exert a protective effect on glucose metabolism [37]. The effects of beer on preventing diabetes seem to be still controversial. Plasma homocysteine concentration, another novel risk factor, significantly decreased and serum folic acid increased only after the non-alcoholic beer intervention.

Wine polyphenols apparently decrease plasma malondialdehyde concentration, a measurement of oxidative stress status, inhibit LDL-cholesterol particles oxidation and increase activity of several antioxidant enzymes. In addition, there is evidence for anti-inflammatory effects of regular wine consumption. Polyphenol-rich alcoholic beverages such as red wine, but not gin, diminished CRP in plasma, increase serum anti-inflammatory Interleukins (ILs), and decrease lymphocyte and monocyte adhesion molecules and cytokines, molecules that participate in the recruitment and migration of circulating leukocytes into the vascular endothelium, initiating the atherosclerotic process [18,19]. Beer, despite its relatively lower antioxidant and anti-inflammatory activity, also exerts a comparable protective role against CVD. Alcoholic and nonalcoholic beer decrease lymphocyte expression of LFA-1 and Sialyl-Lewis X(SLe^x), as does monocyte expression of SLe^x and monocyte expression of C-C chemokine receptor type 2 (CCR2), as well as E-Selectin, IL-6r, IL-15, RANTES and tumor necrosis factor(TN)-β [20]. Finally, beer and de-alcoholized beer also increase circulating endothelial cells, bone-marrow derived stem cells with the ability to repair and maintain endothelial integrity and function (Fig. 4) [38].

On the other hand, a large body of studies addressing this issue has been based on *in vitro* assays and animal studies, which have shown that the compounds derived

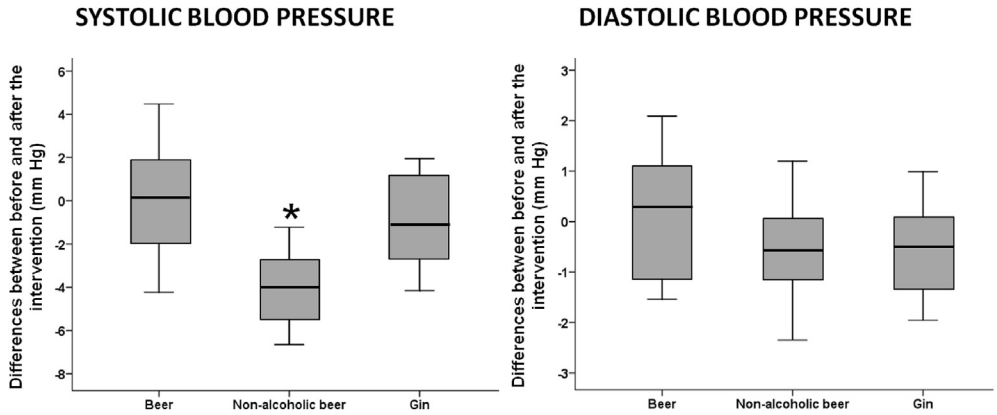

Figure 3 Changes in systolic and diastolic blood pressure observed at baseline and after 4 weeks of intervention with beer (600 mL/d – 30 g/alcohol/d), non-alcoholic beer (900 mL/d – same amount of polyphenols as beer with alcohol intervention) and gin (92 mL – same amount of alcohol as beer with alcohol intervention) in 33 asymptomatic subjects at high risk. Notice that only the reduction in systolic blood pressure after non-alcoholic beer achieved statistical significance compared to the other two interventions (*$P = 0.007$, t test between before and after the intervention). Reprinted with permission from Chiva-Blanch et al. [20].

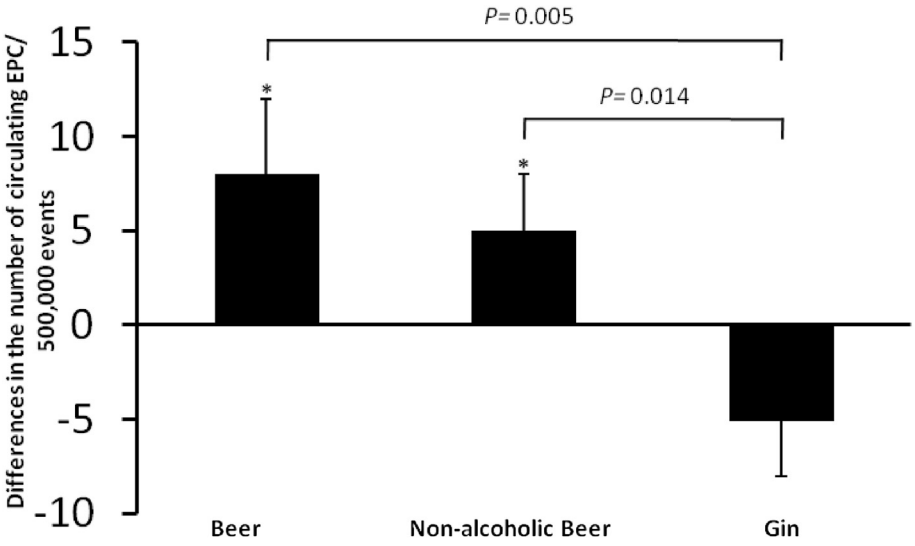

Figure 4 Changes in the number of circulating Endothelial Progenitor Cells (EPC) observed at baseline and after 4 weeks of intervention with beer (600 mL/d – 30 g/alcohol/d), non-alcoholic beer (900 mL/d – same amount of polyphenols as beer with alcohol intervention) and gin (92 mL – same amount of alcohol as beer with alcohol intervention) in 33 asymptomatic subjects at high risk. Notice that the number of EPC is significantly higher after beer and non-alcoholic beer than after gin interventions ($P = 0.008$). *Significant differences between before and after the interventions (*t* test). Reprinted with permission from Chiva-Blanch et al. [38].

from benzoic and cinnamic acids, catechins, procyanidins, humulones and prenil-chalcones are the major contributors to the antioxidant capacity of beer. It has also been observed that xanthohumol inhibited the oxidation of LDL *in vitro* induced by Cu^{2+}, as well as lipid peroxidation of liver microsomes in rats. Finally, the anti-inflammatory effects of bioactive compounds of beer are mainly due to the inhibition of inducible nitric oxide synthase and inhibition of the activity of cyclo-oxygenase 1 [21].

Beer consumption and cancer risk

Beer is the most common type of alcoholic beverage worldwide, and is therefore responsible for a substantial proportion of alcohol-related neoplasms and deaths, although no specific estimate is available for beer only. It is difficult, in fact, to disentangle the possible role of beer drinking separately or in combination with other alcoholic beverages. This is essentially due to the fact that, in several populations, heavy drinkers tend to use more than one type of alcoholic beverage, and the role of (moderate) beer drinking is difficult to analyze and disentangle in any single study, particularly after adjustment for other alcoholic beverages. In addition, data on moderate drinkers of beer only are sparse in most populations.

Using estimates of cancer incidence and deaths and relative risks (RR) for alcohol-related neoplasms from two large meta-analyses including approximately 600 studies and 200,000 cases of various alcohol-related cancers [39,40], in 2012, a total of about 770,000 alcohol-related cancers was estimated worldwide (5.5% of the total). Of these, 536,000 (7.2%) were in men, and 233,000 (3.5%) in women. Corresponding figures for cancer deaths were about 480,000 (5.8% of total deaths) in both sexes combined – over 360,000 men (7.8%) and over 115,000 (3.3%) women [41].

Strong epidemiologic associations with alcohol drinking were observed for cancers of the oral cavity and pharynx, esophagus and larynx, with RRs around 5 for an amount around 50 g/day of ethanol. Direct relations were also observed for cancers of the colon and rectum, liver, breast and (for high doses only) pancreas. For all alcohol-related cancers, there is a clear dose–risk relationship, while the role of duration of – and of stopping – drinking is less clear and more difficult to investigate and quantify [42,43].

Most alcohol-related cancers (85–90%), in fact, are due to heavy drinking (>2 drinks per day in men, >1 in women), while moderate drinking is associated to about 50–60,000 cancer cases and 30–40,000 deaths per year worldwide. Light drinking is associated with oral and pharyngeal cancers (RR about 1.2), esophageal (RR about 1.3) and breast cancer (RR 1.06) [39]. No association was observed for other alcohol-related cancers, including larynx, colorectum, pancreas and liver [44]. It is also possible that under-reporting of alcohol by subjects with greater use may at least in part explain the increased risk of selected cancers from light drinking [45]. There is also a strong interaction between alcohol and tobacco on upper digestive and respiratory tract neoplasms with a multiplicative effect between the two factors [46], but alcohol per se has an independent effect on those cancer sites [47].

For similar doses, the RR of alcohol-related cancers tend to be higher in Asian than in Caucasian or Black populations, and beer is the most common alcoholic beverage in Asia. In a meta-analysis of all available data on oral and pharyngeal cancers up to 2010 [48] the RR for moderate alcohol drinking of all alcoholic beverages (1–2 drinks per day) was 1.62 (95% CI 1.26–2.08) in studies from Asia as

compared to 1.27 (95% CI 1.08–1.50) in those from America and Europe. A similar meta-analysis on colorectal cancer [49] gave a pooled RR for heavy drinkers of 1.81 (95% CI 1.33–2.46) for studies conducted in Asia versus 1.16 (95% CI 0.95–1.43) for studies conducted in Europe.

However, rather than due to specific or stronger associations for beer as compared to other alcoholic beverages, such elevated RRs in Asia may be related to acetaldehyde dehydrogenase (ALDH) polymorphisms in East Asian populations. Some of these (rs671, Glu504Lys), in fact, modify individual differences in acetaldehyde-oxidizing capacity. This leads to the consequent accumulation of acetaldehyde, the first metabolite of alcohol and a recognized carcinogen [50–52]. Subjects with variant ALDH, therefore, even if not heavy drinkers, have higher alcohol-associated RRs than subjects without this polymorphism, if moderate drinkers. This mechanism may well explain the higher alcohol-related RRs in Asian as compared to Caucasian or Blacks. There are therefore no valid data to indicate that beer is associated to higher cancer risk than wine or spirits in Asia.

With reference to other areas of the world, in studies conducted in Denmark beer drinkers had higher RR of lung and upper digestive cancers as compared to wine drinkers [53,54]. The RR of lung cancer for the highest beer consumption level (>2 drinks per day) was around 2, while that for wine (much less frequently consumed in that population, particularly in the past) was below unity. Lung cancer is however not clearly related to alcohol, pointing to a role of residual confounding by tobacco and other correlates of social class [55]. Likewise, the RR of upper digestive tract cancers for the highest level of predominantly beer intake was 4.3, while there was no consistent association with other types of alcoholic beverages in that Danish population. This may, however, be largely or totally due to residual confounding by socioeconomic status (and its major correlate, tobacco), since in Denmark wine tend to be selectively consumed by higher social class individuals. Indeed, Italian data [56] showed higher RR for wine than for beer and other alcoholic beverages on the risk of oral cavity and esophageal cancers. In Italy, wine is the most common type of alcoholic beverage, and is frequently consumed by lower social class individuals.

A network of Italian and Swiss case–control studies considered the role of different types of alcoholic beverages on the risk of head and neck (HN) and esophageal cancers (Table 3) [57–59]. Moderate amounts (up to 2 drinks/day) of beer drinking were not associated to any significant excess risk of these neoplasms, and that no appreciable heterogeneity of risk was observed between beer, wine and spirits. The RRs for moderate beer drinkers were 1.2 for oral, 1.0 for esophageal and 1.7 for laryngeal cancer, and none of these estimates were significant. For heavy beer drinking, the RR of oral cancer was 2.3 (95% CI 1.4–3.2). The associations for spirits were similar to those of beer, whereas the RRs for heavy wine drinkers were much higher (RR = 16.1 for oral and pharyngeal, 17.9 for esophageal, 4.3 laryngeal cancer).

The highest RR for wine is due to the appreciably greater consumption of wine in southern European populations. There is also an inherent difficulty in disentangling the role of different beverages, since, as already mentioned, most heavy drinkers consume more than one type of beverage.

A meta-analysis of all available epidemiological data on oral and pharyngeal cancers up to 2010 [48] gave a pooled RR for moderate drinkers of 2.1 for wine, 2.4 for beer and 2.3 for spirits. For heavy drinkers, the RRs were 4.9 for wine and 4.2 for beer. So far, no adequate data was available for spirits only.

Studies conducted in northern Europe found an excess risk of colorectal [60] and pancreatic [61] cancers, with a specific association with heavy beer drinking. Subsequent studies from southern Europe [62,63], however, did not confirm such specific associations with beer, again suggesting that heavy beer drinking in northern (but not southern) Europe was a correlate of low socioeconomic status, and possibly tobacco smoking. Hence, residual confounding by socioeconomic status, and consequently tobacco, may explain that apparent association. Recent data confirm that heavy alcohol drinking, including beer drinking, is related to colorectal cancer risk, but the association is modest for moderate drinkers, and there is no specific relation with beer rather than other alcoholic beverages [49,64].

Thus, in each population the most commonly used type of alcoholic beverage appears to be the major determinant of heavy drinking, and hence the one most strongly related to cancer risk, in the absence of material difference in RR across types of beverages [56].

In conclusion, there is no evidence that heavy beer drinking is more (or less) harmful on cancer risk than other types of alcoholic beverages. The message therefore remains that moderate alcoholic drinking (up to 1 drink per day in women, up to 2 in men of all types of alcoholic beverages combined) is associated with a modest excess risk of oral and pharyngeal, esophageal and breast cancers [40]. The total amount of ethanol remains the key determinant of an individual subsequent cancer.

Beer consumption and liver function

The specific mechanisms through which beer and its minor components may affect the liver are not fully understood and poorly elucidated.

Laboratory and animal experimental studies

A quantity of 0.5 mL beer/day for 3 months was able to counteract the oxidant action of aluminum toxicity in NMRI mice (aluminum was used as it is considered a substance with powerful pro-oxidant activity, which might be explained by the formation of an aluminum superoxide). At the end of a 30 day experiment, the mice treated with both aluminum and beer showed significantly lower markers of oxidation and TNF-α RNA expression than aluminum treated mice; in addition beer prevented

Table 3 Relative risks (and 95% confidence intervals) of oral cavity, esophageal and laryngeal cancer in drinkers of beer and other types of alcoholic beverages. Italy and Switzerland, 1986–2000.

	Oral cavity and pharynx Altieri et al., 2004 [58] (749 cases, 1772 controls)	Esophagus Bosetti et al., 2000 [57] (714 cases, 3137 controls)	Larynx Garavello et al., 2006 [59] (672 cases, 3454 controls)
Beer, drinks per day			
Non drinkers	1	1	1
1–2	1.2 (1.0–1.5)	1.0 (0.8–1.2)	1.7 (0.7–4.5)
≥3	2.3 (1.4–3.7)		1.8 (0.3–11.2)
Wine, drinks per day[a]			
≤2	1	1	1
3–4	2.2 (1.6–3.0)	1.7 (1.1–2.5)	0.9 (0.6–1.4)
5–7	7.1 (5.0–10.1)	4.2 (2.7–6.6)	1.7 (1.0–2.9)
8–11	11.8 (8.1–17.2)	8.8 (5.4–14.2)	3.9 (2.4–6.3)
≥12	16.1 (10.2–25.3)	17.9 (6.6–48.9)	4.9 (1.8–13.4)
Spirits, drinks per day			
Non drinkers	1	1	1
1–2	1.0 (0.8–1.2)	1.0 (0.8–1.2)	0.9 (0.7–1.1)
≥3	1.9 (1.1–3.3)	1.5 (1.0–2.4)	1.2 (0.7–2.0)

[a] Wine only, whenever available.

accumulation of lipid damage and beer treated mice showed a 40% lower level of aluminum than aluminum treated mice [65]. Studies *in vitro* have shown that beer components may increase the antioxidant capacity of the human serum [66], reduce the formation of Reactive Oxygen Species (ROS) in peripheral blood mononuclear cells [67] and prevent the induction of pre-neoplastic lesions and DNA damage in liver and colon of rats treated with heterocyclic aromatic amines [68].

Experimental studies in humans

There are only limited data from human studies investigating the effect of beer drinking on liver enzymes. Two independent small cross-over trials indicated that up to 4 beers/day do not affect liver enzymes significantly. No evidence of an increase in gamma-glutamyltransferase (GGT), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) after 3 weeks of daily intake of four beers was found in 11 men [69]. Romeo et al. confirmed the lack of an effect on AST, ALT and GGT after consumption in moderation of 1 beer/day in women and 2 beers/day in men for a period of 30 days [70].

However, Sierksma et al., in a small cross-over trial of 10 men consuming 4 beers/day and of 9 post-menopausal women consuming 3 beers/day for a period of three weeks, found a slight increase of GGT and ALT but only in women [71]. An anti-inflammatory action through decreased levels of CRP and fibrinogen was reported as well in both sexes.

Ecological studies

Four ecological studies investigated the relationship between beer consumption and mortality due to liver cirrhosis. In a 1962 report focusing on 46 States from the USA, liver cirrhosis mortality was more strongly associated with wine consumption than either beer or spirit [72]. A positive and significant population–level association between beer consumption and mortality for liver disease was found in 221 municipalities in the State of Louisiana [73]. The relationship between estimates of alcohol use from specific beverages and mortality from liver cirrhosis was analyzed in eight regions of Mexico and a positive association was found with consumption of spirits and pulque (an alcoholic beverage made from the fermented sap of the agave plant), but not beer or wine [74]. Finally spirit consumption was the strongest correlate of cirrhosis mortality in a pooled cross-sectional time-series analysis of data from a group of English-speaking countries from 1953 to 1993 [75]. The cost of the specific alcoholic beverage in different parts of the world and its relationship with heavy alcohol use might explain some of the findings from these ecological studies.

Epidemiological studies

While numerous studies on the relationship between specific alcoholic beverages total or cardiovascular mortality have been published, only two studies are available on the longitudinal relation between beer drinking and liver health. In a cohort of 36,350 healthy men from eastern France, consumption of up to five beers/day was not associated with an increased mortality due to cirrhosis. Whereas, daily intake of more than 55 g of alcohol was associated with an increased risk [76]. In a Danish cohort of 30,630 men and women high intake of all 3 types of alcohol was associated with an increased risk for liver cirrhosis. However, wine drinkers had lower risk than beer and spirits drinkers [77]. Other studies did not find significant differences in the effects on liver determined by different types of alcoholic beverage, i.e. beer vs. wine or spirits [78].

To date, there is limited information regarding the specific association between consumption of beer and liver function/health. It is clear that excessive use of beer (as for any alcoholic beverage) is detrimental to health and that beer (as other alcoholic beverages) should be used in moderation. So far, there is no evidence that beer is more deleterious or has more benefits compared with other sources of alcohol. Alcohol apparently remains the most powerful biological agent in any alcoholic beverage.

Beer consumption, cognitive impairment and dementia

Dementia is a major public health concern in modern societies. Its prevalence increases with age, especially after 65 years, and about 20% of the individuals aged 80 years or older are affected. The most frequent type of dementia is Alzheimer's disease that is associated with high levels of morbidity, mortality and socio-economic costs. With the aging of the population, the prevalence of dementia is expected to increase significantly. Since there is no established treatment or preventive measure, delaying its onset through the identification of risk factors associated with dementia and Alzheimer's disease is crucial. Actually, lifestyle habits have been considered to play a key role in reducing the risk burden of such disease, and among these, alcohol consumption has been extensively studied in relation to the occurrence of dementia in recent years, with conflicting results [79].

Alcohol has been postulated to act as a neuroprotective factor through different mechanisms [80]:

- First, as already mentioned above, it might act through reduction of cardiovascular risk factors, either through an inhibitory effect on platelet aggregation, or an alteration of the serum lipid profile. In actual fact, randomized crossover dietary studies demonstrated that alcohol intake is able to raise HDL-cholesterol, insulin sensitivity, and ameliorate inflammatory pathways.
- Second, alcohol has been found in experimental studies to initially increase hippocampal acetylcholine release, which is associated with an improvement of memory performance.
- Third, alcohol use has been inversely associated with dementia through protective changes in cerebral vasculature. Indeed, light-to-moderate alcohol use has been associated with a lower prevalence of MRI-defined white matter lesions and sub-clinical infarcts. However, the inverse association of alcohol use with dementia has been found to be more relevant among subjects not carrying the APOE e4 allele, who are at lower risk of dementia.

Over the last years, despite an increasing interest on the possible association between alcohol consumption and neurodegenerative disease, only few analytical studies (7 in total, of which 3 were nested case–control and 4 cohort prospective studies) have reported data on beer consumption [81]. The studies showing the possible association between beer consumption and neurodegenerative outcomes are reported in Table 4 [82–88]. As far as case–control studies are considered, data are available from 3 studies analyzing subjects living in 3 different countries (Denmark, Canada and U.S.). In the Copenhagen City Heart Study, data on alcohol consumption collected in 1976 was linked to the risk of dementia after 15–18 years of follow-up. Compared to never or hardly ever drinkers, the risk of developing dementia was significantly lower for monthly and weekly intake of wine but not for daily intake. With regard to beer consumption, a non-significant association was found for weekly (OR 2.13; 95% CI: 0.98–4.78) and daily intake (OR 1.73; 95% CI: 0.75–3.99), while a significant increased risk was observed for monthly intake of beer (OR 2.28; 95% CI: 1.13–4.60).

Later, the Canadian Study of Health and Aging, which investigated the risk of developing dementia in 4088 subjects followed for 5 years, obtained similar results. The risk was decreased for total alcohol consumption, but the greater reduction was observed in wine drinkers (OR 0.49; 95% CI: 0.28–0.88), with respect to beer drinkers (OR 0.84; 95% CI: 0.51–1.41) and spirit drinkers. A null association with beer consumption was also evidenced in a nested case–control study of 373 cases with incident dementia and 373 controls analyzed through neurological and neuropsychological examinations within the cohort of the Cardiovascular Health Study. Self-reported usual weekly intake of total alcohol, compared with abstention, was associated with a significant reduced risk of dementia. However, when total alcohol was analyzed for its different beverage types (beer, wine, liquor), no significant association was revealed.

With regard to cohort prospective studies, data on beer consumption were available from 4 studies for subjects living in 3 different countries (The Netherlands, USA and China). In 2002, the association between alcohol consumption and dementia was analyzed in the participants of the Rotterdam Study. The cohort comprised 7983 subjects aged 55 years or over who developed, after 6 years of follow-up, 197 incident cases of dementia. The risk of dementia were significantly decreased among subjects who drank 1–3 drinks per day, but when type of alcohol was taken into consideration, no difference was observed for all the studied types of beverage, including beer.

Another cohort study, which investigated the association between total alcohol and specific types of beverage, was the Washington Heights Inwood–Columbia Aging Project, conducted in New York City, 980 community-dwelling individuals aged 65 and older without dementia at baseline were studied for their alcohol consumption and followed for 4 years afterwards. After 4 years of follow-up 260 individuals developed dementia (199 Alzheimer's disease and 61 dementia associated with cerebrovasular disease). The results, at a multivariable model adjusted for all the possible confounders, showed an association between light-to-moderate alcohol consumption and lower risk of dementia and Alzheimer's disease, but non-significant association for beer consumption was evidenced.

Table 4 Studies investigating the association between beer consumption, dementia, Alzheimer's disease and cognitive impairment.

Study (Cohort)	Type	Patients, *n*	Outcome	Categories of consumption	Results	Adjustment
Truelsen et al., 2002 (*Copenhagen City Heart Study*) [82]	Nested case–control study	83 with dementia 1626 nondemented subjects	Dementia	Never/hardly ever Monthly Weekly Daily	-1- 2.28 (1.13–4.60) 2.15 (0.98–4.78) 1.73 (0.75–3.99)	Age, sex, education, history of stroke, income, blood pressure, smoking habit
Ruitenberg et al., 2002 (*Rotterdam Study*) [83]	Prospective study	7983 nondemented subjects 197 incident dementia	Dementia	<1 drink per week ≥1 drink per week 1–3 drinks per day	N.R.	N.R.
Lindsay et al., 2002 (*Canadian Study of Health and Aging*) [84]	Nested case–control study	194 AD patients 3894 cognitively normal subjects	AD	Weekly consumption	0.84 (0.51–1.41)	Age, sex, education
Mukamal et al., 2003 (*Cardiovascular Health Study*) [85]	Nested case–control study	373 incident dementia 373 controls	Dementia	None <1 drink/wk 1–6 drinks/wk ≥7 drinks/wk	-1- 0.84 (0.48–1.47) 0.74 (0.36–1.54) 1.96 (0.71–5.47)	Age, sex, race, apoE, education, income, marital status, estrogen therapy, smoking habit, diabetes, BMI, cholesterol, atrial fibrillation, history of stroke, physical activity
Luchsinger et al., 2004 (*Washington Heights-Inwood Columbia Aging Project*) [86]	Prospective study	980 nondemented subjects 199 AD after 4 yrs	AD	None Light-to-moderate	-1- 1.39 (0.95–2.06)	Age, sex, education, apoE
Deng et al., 2006 (*Chonhqing City*) [87]	Prospective study	2632 nondemented subjects 121 incident dementia after 2 yrs	Dementia	Non-drinker Light-to-moderate Excessive drinker	-1- 2.47 (1.23–4.96) 1.96 (0.43–8.93)	Age, sex, education, blood pressure, smoking habit, history of stroke, MMSE score
Weyrer et al., 2011 [88]	Prospective study	3202 nondemented subjects 217 incident dementia after 3 yrs	Dementia AD	Consumption Consumption	0.87 (0.56–1.35) 0.60 (0.30–1.21)	Age, sex, education, depression, apoE, smoking habit

Abbreviation: AD, Alzheimer's disease; N.R., Not reported; BMI: Body Mass Index; MMSE: Mini-Mental State Examination.

Conversely, a significant increased risk of dementia for beer consumption was reported in a 2-year prospective study conducted in a cohort of elderly people from six communities in China [87]. The cohort comprised 2632 participants who developed, after 2 years of follow-up, 121 incidental cases of dementia. By grouping subjects according to alcohol consumption into three categories, non-drinkers, light-to-moderate and excessive drinkers, the study reported a significant protection for light-to-moderate consumption of total alcohol (OR 0.52; 95% CI 0.32–0.85) versus occurrence of all types of dementia. However, when specific types of alcohol beverage were taken into consideration, light-to-moderate consumption of wine was related with a reduced risk of dementia (OR 0.68; 95% CI 0.50–0.92) while light-to-moderate consumption of beer was associated with a significantly increased risk of dementia than that of non-drinkers (OR 2.47; 95% CI 1.23–4.96).

Finally, results from a 3-year follow-up prospective study conducted among primary care attenders aged 75 years and older in Germany were reported [88]. The cohort included 3202 subjects free of dementia that were studied at baseline, 1.5 years and 3 years later. Incident overall dementia was diagnosed in 217 of them. Significant inverse relationship was found between total alcohol consumption and incident overall dementia (HR 0.71; 95% CI 0.53–0.96) for consumers vs. abstainers, but no significant association was found for subjects who reported that they drank only beer for the occurrence of overall dementia (HR 0.87; 95% CI 0.56–1.35) and Alzheimer's disease (HR 0.60; 95% CI 0.30–1.21).

In conclusion, nested case–control and prospective cohort studies tend to show that moderate alcohol consumption is associated with a reduced risk of developing dementia and Alzheimer's disease [85]. This may however be due to selective stopping alcohol drinking in subjects with cognitive impairment (i.e. reverse causation) However, no clear association between specific type of alcohol beverage and dementia has been evidenced. In particular, the existing literature on beer consumption, although very limited with respect to that available for wine consumption, reports no clear association between beer and dementia or mild cognitive impairment. Specific and larger studies are warranted to clarify this issue.

Beer consumption and total mortality

Low alcohol intake is inversely related to vascular disease, but the other side of the coin shows an increased risk of certain cancers, cirrhosis and death from accidents associated with increasing alcohol consumption [89]. As a consequence, even at lower dosages the benefit of alcohol could be overcome by its harmful effects [38,90]. This hypothesis was tested in a meta-analysis including 34 prospective studies on alcohol and all-cause mortality [89] that pooled findings from more than one million adult (aged $\geq$ 18 years) healthy subjects and about 95,000 deaths from any cause. The J-shaped relationship observed between total mortality and increasing amounts of alcohol consumed indicates that low to moderate consumption of alcohol ($\leq$1 drink/day in women and $\leq$2 drinks/day in men) significantly reduces total mortality, while higher doses increase it [89]. The pooled curves for males and females were different for the range at which alcohol remains protective (protection in women disappeared at doses lower than in males) but comparable (17–18%) regarding the maximum protection [89]. Maximum risk reduction in males was lower in USA (14–19%) as compared to Europe (20–28%); the protection extended up to 6 drinks/day in European but only up to 3 drinks/day in USA studies [89].

A similar effect was observed in cardiovascular patients: in a meta-analysis on mortality for any cause [25,91], based on 7 studies comprising 16,398 CVD patients, J-shaped pooled curves were observed in the overall analysis (average maximal protection 18% in the range of 5–10 g/day) and in all subgroups according to either the type of patients or characteristics of the studies.

These findings originate from two meta-analyses based on alcohol intake from any type of alcoholic beverages. Specific data on the link between beer and total mortality are scarce.

- In a study conducted in eastern France [76] (36,250 healthy men, 12–18-year follow-up, 3617 deaths) drinking wine or beer in moderation reduced the risk of cardiovascular death, but only wine was associated with a lower all-cause mortality.
- In a study conducted among 7735 British men aged 40–59 years [92] (17 years of follow-up, 1308 deaths from all causes) regular beer drinking was associated with a reduction of total mortality with a HR equal to 0.84 (95% CI: 0.71–1.01), in comparison with occasional drinkers.
- In The Copenhagen City Heart Study [93] (270,505 person years of follow-up, 7208 people deaths for any cause), only a monthly intake of beer was found to be associated with a slightly lower mortality. Persons with a daily intake of beer in excess of two drinks carried an increased risk of death compared with never beer drinkers.
- In the EPIC Study [94] (380,395 men and women, followed up for 12.6 years on average, 20,453 fatal events) lifetime never beer users displayed higher risks than moderate drinkers. However, in women, beer use was more strongly related than wine to overall mortality for amounts greater than 3 g/day compared with the reference category (0.1–2.9 g/day).

In conclusion, evidence suggests a J-shaped relationship between alcohol consumption and total mortality, with lower risk for moderate alcohol consumers [22,89,91]. Specific data on beer are not conclusive, although some results indicate a positive role of drinking beer in moderation (1 drink/day, about 12 g of ethanol) against mortality for any cause [94]. Heavy alcohol (and beer) consumption increases the risk of total mortality [89], ranking in the

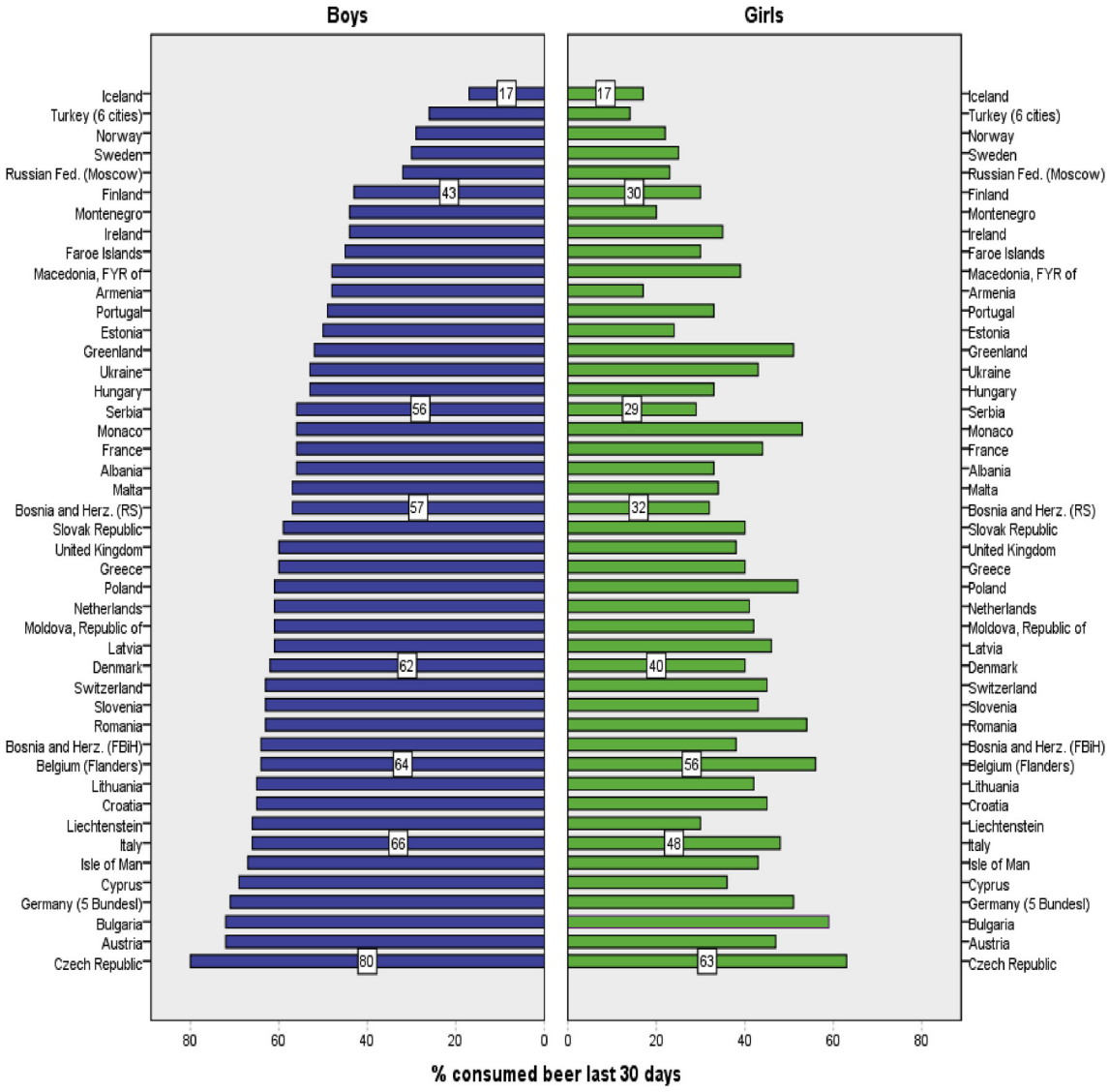

Figure 5 Proportion of adolescents having consumed beer during the last 30 days by gender and country. Source: ESPAD data, 2011 [102].

Table 5 Comparison of beer drinking patterns in three countries by age and sex.

Country	Available indicators	Men				Women			
		16–24	25–44	45–64	65+	16–24	25–44	45–64	65+
United Kingdom	*Drinking: adult's behavior and knowledge, report, 2009* [106]								
	Percentage of drinks/week								
	Strong beer[a]	23	10	12	8	11	4	3	2
	Light beer[a]	45	54	46	35	12	18	17	9
	Beer (both)[a]	68	64	58	43	23	22	20	11
Italy	*"La vita quotidiana nel 2009"* [107]								
	Prevalence of beer consumption	62	74	69	38	38	44	37	15
	Daily beer consumption	8	11	8	3	2	2	1	1
Luxembourg	*ORISCAV-LUX 2007–2008* [105]								
	Percentage of drinks/week	18–24	25–44	45–64	65–69	18–24	25–44	45–64	65–69
	Strong beer[a]	12	5	5	4	5	5	2	0
	Light beer[a]	44	35	22	32	26	13	6	10
	Beer (both)[a]	56	40	27	36	31	18	8	10
	Prevalence of beer consumption (%)	70	76	70	58	36	29	25	24
	Daily beer consumption (%)	0	7	11	11	0	1	0	5

[a] Only those that declared that they drunk at least one alcohol beverage were included.

eighth place among the causes of attributable deaths all over the world [95].

Conclusions

Low to moderate (up to 1 drink -equivalent to about 12 g of ethanol- per day in women, up to 2 in men of all types of alcoholic beverages combined), non-bingeing beer or wine consumption, in the absence of specific contraindications and in the context of healthy eating and a healthy lifestyle, significantly reduces the risk of CVD. Less clear-cut evidence is available for stroke, possibly due to the heterogeneity of this clinical condition.

Epidemiological studies suggest that regular and moderate consumption of fermented beverages (wine and beer) confer greater cardiovascular protection than spirits. Part of the protective effects of beer and wine is due to their alcoholic content and part to their non-alcoholic components (mainly polyphenols).

There is limited information regarding the specific association between low to moderate consumption of beer and liver function. Low to moderate alcohol consumption is associated with a reduced risk of developing neurodegenerative disease but the existing literature on beer consumption is not conclusive.

Although regular, moderate alcoholic drinking is associated to a modest excess risk of oral and pharyngeal, esophageal and breast cancers, there is no evidence that beer drinking is different from other types of alcoholic beverages in respect to this particular cancer risk.

Evidence suggests a J-shaped relationship between beer or wine consumption and all-cause mortality, with lower risk for light to moderate alcohol consumers than for abstainers or heavy drinkers.

The studies examined for the present Consensus are primarily of European or US origin. Little evidence is available from Asian, African or Latin American/Southern American studies.

Unless they are at high risk of alcohol-related cancers, there is no reason to discourage healthy adults who are already regular light-moderate beer consumers from continuing to follow the same pattern. On the other hand, we do not recommend that adult life-long abstainers begin drinking for health reasons as, up to now, there is no direct evidence that adult abstainers who start drinking beer or other alcoholic beverages (also in moderation) reduce their risk of chronic diseases.

Excessive alcohol (beer) consumption exerts deleterious effects on the human body, with increased risks for many organs, but most primarily for the liver. In addition, there are social problems such as addiction, accidents, violence and crime.

Data reported in this document show evidence for no harm of moderate beer consumption for major chronic conditions and some benefit against cardiovascular disease.

Consumption of any alcoholic beverage, at any dosage, is not recommended for children, adolescents, pregnant women, individuals at risk of alcoholism, those with cardiomyopathy, cardiac arrhythmias, depression, or liver and pancreatic diseases, or during performing actions that require concentration, skill or coordination.

Health messages extrapolated from this consensus document should be integrated within specific socio-cultural contexts in different Countries.

Conflict of interest

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Appendix. Additional aspects of beer consumption

Beer consumption among different age groups and countries

The potential beneficial effects of alcohol consumption are conferred only by moderate consumption in healthy adults, whereas heavy consumption is harmful and associated with several chronic health problems [96–98]. There is no

evidence that alcohol provides health benefits in the young, rather the opposite. The effects of alcohol on young people are not the same as they are on adults. While alcohol misuse can present health risks in all age groups, it is even more dangerous for children and adolescents [99,100].

National surveys-based data: adolescents and young adults (16–24 years)

The European School Survey Project on Alcohol and Other Drugs (ESPAD-2011), conducted among 100,000 students in 36 European countries in 2011, reports that beer is the preferred beverage for boys and spirits for girls aged 15–16 years old [101,102]. An inter-country variation exists with more than 60% of adolescents having consumed beer in the last 30 days in Belgium, Germany, Bulgaria and Czech Republic, 40% in the Baltic States and 17% in Iceland (Fig. 5). Among students reporting "any last day alcohol consumption", about 52% of them did not drink beer, 37% had a moderate consumption and 11% had more than 1 L of beer. Among 17–18 years old students a large inter-country variation is also reported, with the highest prevalence in Poland (80%), and the lowest in France (50%). Overall, boys consume more alcohol than girls in all countries [103].

Country-specific analysis of ESPAD data reported that adolescents seeking to have fun and get drunk do prefer beer or spirits. However after adjusting for the effect of drinking motives, the beer preference does not remain significantly related to risky drinking but spirit preference does. Therefore developing approaches that target adolescents that prefer spirits is recommended for prevention [104]. Among adolescents, national legal age for sales of alcohol beverages is likely to account for some of the observed differences across countries; the high prevalence in the last 30 days of beer consumption in countries with a lower age limit stresses the importance of alcohol restrictive policies.

Table 5 depicts a comparison of beer drinking patterns in three countries by age and sex [101,105–107]. Italian and Luxembourgish data show similar sex-specific difference for beer consumption among adolescents and young adults (up to 24 years old) with 38%, 36% of women and 70%, 62% of men drinking beer, respectively. While there are no daily consumers in Luxembourg, 8% of men and 3% of women drink beer every day in Italy. Concerning weekly beer consumption, making up 68% of weekly drinks in the UK and 56% in Luxembourg, beer is the most consumed beverage among British and Luxembourgish young men but is less popular among young women (31% and 23%, respectively).

A recent survey on Italian young people (under 24 years old) has reported a progressive decrease of both beer and wine consumption starting in 2006. Such a reduction was apparent in both sexes especially for drinking in public spaces rather than at home [108].

Adults (25+ years)

According to the survey on cardiovascular risk factors (ORISCAV-LUX) and the European Health Interview & Health Examination Surveys Database [101,105] beer is very popular among adult men in Europe, as represented by Luxembourg and Italy. About 70–76% of 25–64 years old Luxembourgish and 69–74% of 25–64 years old Italians drink beer. After the age of 65, popularity of beer drops to 58% in Luxembourg and to 38% in Italy. The proportion of men drinking beer daily increases with age in Luxembourg: from 7% of men aged 25–44 years to 11% after 44 years old. In Italy only 3% of men drink beer every day after their 65th anniversary, whereas among younger men this percentage increases from 8 to 11%. Beer is less popular among women and that popularity drops with age in both countries. While daily consumption concerns only 5% of older women in Luxembourg, in Italy it remains at 1–2% across all ages (Table 5). Beer accounted for 58–64% of weekly drinks among 25–64 years old British men. This percentage drops to 43% among older ages. Among British women, about 1 in 5 alcoholic drinks per week is beer, except for the 65 years or older group, in whom 1 in 10 drinks is beer. Among Luxembourgish men beer is less popular with 40% of weekly drinks among 25–44 years old; it drops to 27% among 44–64 years old and increases to 36% among older men. Light beer is the most preferred beverage in all ages in UK whereas in Luxembourg, trends for both light and strong beers are similar.

Alcohol sales data, retrieved from WHO reports, indicate that among different types of alcohol consumption, wine is the most popular alcoholic beverage consumed in Italy, Luxembourg, Spain and France and beer in the UK, although wine preference is increasing [109]. In 2010, beer constituted 37% of the recorded per capita alcohol consumption (15+) in the UK, 36% in Luxembourg, and 23% in Italy [109]. Annual per capita beer consumption from 1960 to 2010 was stable in Italy (around 2.3 L of pure alcohol), and in Luxembourg (around 5 L of pure alcohol). In the UK beer consumption increased from 6 to 8 L in 1979 and dropped below 5 L of pure alcohol in 2010. For beer that contains 5% of alcohol by volume, 1 L of pure alcohol corresponds to 20 L of beer.

Based on country specific policies from five regulatory domains – physical availability of alcohol, drinking context, alcohol prices, alcohol advertising, and operation of motor vehicles – an Alcohol Policy Index (API) score has been validated [110]. Among the three countries, Luxembourg was scored as having the least restrictive policies whereas UK was the most restrictive. A less restrictive alcohol policy at country level was significantly associated with higher per capita alcohol consumption. However, the association was based on cross-sectional data, precluding the possibility to draw conclusions about the causality of the relation. The annual sales of pure alcohol liters/person older than 15 years do not give details on age, gender variations and drinking patterns. Given the relatively high quantities of alcohol bought by non-residents, consumption might be over-estimated in small countries. The API score provides ranking of countries and benchmarking is possible based on their specific alcohol policy control.

The WHO uses the Patterns of Drinking Score (PDS) to account for the impact and the multidimensionality of alcohol consumption on health [109]. Several drinking attributes like the usual quantity of alcohol consumed per occasion; festive drinking; proportion of drinking events when drinkers get drunk; proportion of drinkers that drink daily (or nearly daily); drinking with meals; drinking in public places, are weighted differently and combined into the PDS. Two attributes, drinking with meals and proportion of drinkers that drink daily make patterns of drinking less risky [111]. The most risky patterns of alcohol consumption, PDS score 5 in a scale of 1–5, are reported in Russia and in Ukraine. This burden of disease-related measure estimates a risk score 1 for Luxembourg and Italy and 3 for UK. This is in line with international literature emphasizing major cultural and social differences across Europe in the way alcohol is consumed (i.e. drinking patterns), with Northern European countries showing more risky alcohol behaviors than their Southern counterparts, i.e. a North-to-South gradient [112]. Luxembourg, despite its geographic location, is populated by large southern European communities, primarily Portuguese and Italians.

In conclusion, beer is a very popular alcoholic beverage among teenagers and younger adults, whereas its appeal seems to decline with increasing age, although with considerable inter-country variations. Methodological issues and inconsistencies in assessing beer intake across surveys make international comparisons challenging.

Beer consumption in the context of the mediterranean diet

A Mediterranean dietary style is associated with a healthier and longer life in Western societies, when compared with other dietary patterns. Moderate alcohol consumption is part of the Mediterranean diet, with wine as the typical alcoholic beverage choice. Although preference for beer is more common in non-Mediterranean populations, the use of beer is not trivial also in Mediterranean countries and the question of the impact on health of its use in these populations is an intriguing one. It may provide information on some relevant questions: a) is wine the specific “good” alcoholic beverage especially for CHD?; b) is the beer drinking pattern, most common outside the meal or even as a binge habit, a marker of a “dangerous drinking style ” also in Mediterranean populations?

In addition, the evaluation of the relationship between the socio-cultural environment and the prevalence of alcoholic beverage preference, as is the case of the comparison between Mediterranean and non-Mediterranean populations, may provide information on the potential role of socio-cultural factors as confounders of the effects of alcohol consumption on health [113].

The use of beer as a preferred beverage is typical of populations characterized by higher (compared with Mediterranean populations) frequency of major chronic disease (i.e. CVD and cancer), where other dietary components and other biological characteristics may make the difference [114]. In Italy, Spain, Greece and France the annual per capita beer consumption is between 30 and 40 L, whereas in Central and Northern Europe the consumption varies from 70 to more than 100 L [115]. The preference for beer consumption is described in combination with less healthy habits in many non-Mediterranean as well as in Mediterranean populations: in the UK general population 12% of the budget is dedicated to healthy foods compared with 18% in wine-preferring households [116]; less fruit and vegetables and more soft drinks, meat and fat are bought by beer consumers in Denmark [117]; Finnish women preferring beer have the highest energy intake from saturated fat and sugar [118]. Outside Europe, in US general population surveys beer consumption is associated to a worse Healthy Eating index [119]. In France the highest intake of energy, fat, carbohydrates, high-fat meat, potatoes and snacks has been found in beer consumers [120,121]; in a Spanish study beer drinkers adhere less to the guidelines on fruit, vegetables, meat, fish and eggs consumption [122].

In Spain the beer consumption is increasingly replacing wine in parallel with a change also in the way of eating, that is less adherent to the Mediterranean style [123]. Recent studies on Spanish population samples indicate that the observed change in the way of eating (including the change from wine to beer) is associated with higher prevalence of the metabolic syndrome (especially larger waist circumference) and overweight (more weight gain in life) [124,125]. These findings may be attributed to a general change in dietary habits rather than to the change from wine to beer. Moreover, the finding in the same population that beer consumption, and not wine, is associated with an increase of the prevalence of hypertension may be due to the drinking pattern (outside meals and less moderate) [126]. The evaluation of studies where the Mediterranean dietary style has been analyzed both in Mediterranean and in non-Mediterranean populations has disproved the beer-belly hypothesis, that is the higher probability of increase in waist circumference in beer drinkers. This is likely to occur only with more than 1 L of daily consumption of beer [123] and when the diet is not adherent to the Mediterranean style [127].

The preference for wine has a different pattern of association with dietary components when Mediterranean and non-Mediterranean populations are compared. The association with healthier eating habits is found in the latter and not in the former [113,114]. This may indicate that within a particular population, the use of a specific type of beverage may be determined by socio-economic and cultural conditions, usually independently associated with health outcomes. In the Mediterranean countries wine is consumed commonly at meals in different social classes [115], and the accessibility of this beverage in terms of cost reinforces this picture; whereas more than 60% of the consumed beer occurs in pubs and restaurant rather than at home. In non-Mediterranean countries wine consumption is clearly more common in upper classes due to the higher cost when compared to beer.

Although clinical and epidemiological studies indicate that moderate wine consumption may protect against some chronic disease [17,21,22], the well-established association between social factors and health outcomes [128] suggests that part of this effect in non-Mediterranean populations is mediated by better education and by higher socio-economic status. On the other hand, some unhealthy effects of beer drinking in all populations may be confounded by other dietary habits or by the drinking pattern. However, high quality European investigations on diet and chronic disease including the evaluation of adherence to a Mediterranean diet, which includes moderate alcohol consumption, show that the greater adherence to Mediterranean-like dietary habits is associated with increased longevity, reduced risk of colon cancer and diabetes [129]. More interestingly, Italian studies evaluating the Italian Mediterranean index, built up on specific Italian dietary items that include moderate alcohol consumption as wine or beer, indicate that a lower risk of stroke, and colon cancer, are associated with a greater adherence to the Mediterranean diet [128,129].

We can safely say that the health effects of beer and wine are greater in combination with a healthy diet. We have evidence that moderate beer consumption as well as moderate wine consumption at meals may have some healthy effects in combination with a Mediterranean-type diet, rich in vegetables, whole grains, and fruit [129]. One may speculate that this way of consuming alcoholic beverages favors some synergistic effects between polyphenols in these two alcoholic beverages and other similar compounds of the diet [21].

In conclusion, beer consumption is less preferred than wine in Mediterranean populations, although in some countries (i.e. Spain) beer consumption is becoming more common. The health effect of beer is undistinguishable from that of wine in population investigations where a typical Mediterranean dietary pattern is evaluated. In all populations non-moderate consumption and unhealthy drinking pattern (outside meals and binges) of beer might be responsible for undesirable health effect associated with this beverage.

New generation beer: alcohol-free and gluten-free

Alcohol-free beer

Alcohol-free beer is a non-alcoholic beverage suitable for all populations, even for countries where alcohol is either wholly or partially banned. Contrarily, regular (alcohol) beer consumption has to be avoided in some physiological (pregnancy, sporting professionals, driving, handling dangerous machinery, etc.) or pathological conditions (liver disease, alcoholism, cancer, poly-medication, etc.) as well as for cultural or religious reasons.

Alcohol-free beer has the same bioactive compounds (although in lower concentrations) than regular beer except for alcohol. In alcohol-free beer production, alcohol is removed by (vacuum) distillation, vacuum evaporation, dialysis and reverse osmosis. Therefore, during the de-alcoholization process a significant loss of non-alcoholic components such as polyphenols and other bioactive and aromatic compounds may take place, to an extent depending on the de-alcoholization method [130]. Alcohol-free beer contains about 120 mg/L total polyphenols while regular beer contains 280−520 mg/L [131].

There is no restriction in the daily amount of alcohol-free beer consumption, so it seems feasible to achieve the same total amount of these molecules with less intake of alcohol-free beer than from regular beer. Thus, it brings the question if alcohol-free beer consumption has the same health effects as regular beer without the detrimental (or protective) effects of alcohol itself. In other words, does the non-alcoholic fraction of beer act in the human body independently of its alcoholic part?

Several *in vitro* and animal model studies have tested the biological effects of beer polyphenols. Beer polyphenols (and the non-alcoholic fraction of beer) exert anti-inflammatory [67,132,133] and antioxidant effects [134], act as platelet inhibitors [135], prevent endothelial dysfunction [136] and might be cancer chemopreventive.

In a cross-over trial, 33 men at high cardiovascular risk were randomized to receive beer (30 g alcohol/d), the equivalent amount of polyphenols in the form of non-alcoholic beer, or gin (30 g alcohol/d) for 4 weeks each intervention. In these patients, systolic blood pressure, homocysteine and several biomarkers of inflammation such as E-Selectin, Interleukin (IL)-6r, IL-15, regulated on activation, normal T cell expressed and secreted (RANTES) and Tumor necrosis factor (TNF)-β decreased only after the non-alcoholic beer intervention. After beer and alcohol-free beer interventions, the receptor antagonist of IL-1 increased, and lymphocyte expression of lymphocyte function-associated antigen-1 (LFA-1), lymphocyte and monocyte expression of Sialyl-Lewis X (SLe^x) and monocyte expression of C-C chemokine receptor type 2 (CCR2) decreased [20]. Moreover, moderate alcoholic and non-alcoholic beer consumption enhanced the number of circulating endothelial progenitor cells (Fig. 4) [38], known to repair the injured endothelial layer by differentiating themselves to mature endothelial cells [137].

In 29 postmenopausal women, who during 45 days drank 500 mL/d of alcohol-free beer divided into two doses, lipid profile, inflammatory markers such as C-reactive protein (CRP), IL-1 and IL-6, and TNF-α, and parameters of oxidative metabolism were determined. After the alcohol-free beer period, oxidized LDL, thiobarbituric acid-reactive substances (TBARS) and plasma carbonyl group content decreased. In addition, alpha-tocopherol levels and erythrocyte glutathione levels increased, showing a cardioprotective antioxidant effect of alcohol-free beer consumption [138].

Overall, no synergistic effects were observed between the alcoholic and non-alcoholic fractions of beer, pinpointing that alcohol-free beer is cardioprotective because of its non-alcoholic composition. In some of these studies (not all) cells or animals were overdosed, possibly overestimating the real effects in humans, in whom lower concentrations of dietary polyphenols are usually reached in plasma and tissues.

There is no epidemiological information on the relationship of alcohol-free beer consumption and cancer incidence. In a large cohort, flavonol intake (a group of polyphenols present in beer) reduced the risk for developing pancreatic cancer [139]. The chalcone xanthohumol a characteristic hop-derived polyphenol of beer, protects against DNA damage and liver and colon cancer at physiological concentrations [68]. Antioxidant, anti-inflammatory, antiangiogenic, antiproliferative and anti-estrogenic effects of xanthohumol have been described, affecting various steps of carcinogenesis from tumor initiation to dissemination by several molecular pathways [140,141]. Moreover, 6- and 8-prenylnaringenins, polyphenols also present in beer, have shown anti-proliferative effects in a dose- and time-dependent manner [142].

Thus, taking into account that alcohol-free beer does not contain ethanol, the principal carcinogenic compound of beer, and that beer polyphenols at physiological doses may have (perhaps subtle) anti-carcinogenic effects, it seems plausible that alcohol-free beer might have a modest preventive role in cancer development and progression.

In summary, in view of the effects observed after alcohol-free beer consumption, and taking into account that it is a non-alcoholic beverage for which no detrimental effects have been described, it can be a useful alternative to moderate beer consumption when alcohol consumption is banned or should be avoided. This is of special interest in pregnant or breastfeeding women, as it has been observed that alcohol-free beer is likely innocuous for the breastfed infant [143].

Light beer is another new generation beer whose consumption is still modest but emerging. Light beer is a low-alcohol beer produced by partial de-alcoholization of beer or by impairing alcohol production by yeast. In consequence, people that must avoid ethanol consumption should not consume it. According to its composition one may speculate that light beer consumption may be “in the middle” between the protective effects of beer and the effects of alcohol-free beer when consumed in the same amount as regular beer. However, as it is still an emerging product, no studies have been performed evaluating its effects.

Gluten-free beer

The brewing industry is making efforts to increase its presence in the market and to adapt to special needs of certain groups of individuals. An example of that is the development of gluten-free beers. Celiac disease is a chronic disease precipitated by the ingestion of gluten-containing foods. It consists of a reaction to a sequence of amino acids in prolamins, especially gliadin of wheat gluten, but also hordein in barley that causes lesions in epithelial cells of the small intestine (villi) and as a result, nutrients are poorly absorbed. Although celiac disease affects only approximately 1/100 to 1/300 of the population [144], its prevalence is increasing and its epidemiology has iceberg characteristics: there are more undiagnosed cases than diagnosed cases [145]. In addition, a non-celiac gluten-intolerant population is being defined as those individuals who develop digestive track discomforts during adult life.

Celiac disease is a chronic form of enteropathy, immunologically mediated by T-cells, which affects the small intestine in genetically predisposed subjects; it is triggered by the ingestion of gluten (prolamin)-containing foods [146].

A lifelong strict gluten-free diet is the only currently available therapeutic treatment for patients with celiac disease. Prolamin is the fraction of gluten responsible for the immune reaction in predisposed individuals. In the Codex Alimentaris, prolamins are defined as the fraction from gluten that can be extracted by 40–70% of ethanol. The prolamin from wheat is gliadin; from rye it is secalin, from barley hordein and from oats avenin. In consequence, no foods or medications containing gluten from wheat, rye, and barley or their derivatives can be taken, as even small quantities of gluten may be harmful. Oats are not toxic in >95% of patients with celiac disease, but there is a small subgroup in whom oats are not safe [147]. Therefore the food industry is constantly making efforts to develop processed food products free of gluten.

Beer contains only about 0.3% proteins or polypeptides, the principal source of which is malt. Malt is produced mostly from wheat or barley, which contains prolamins associated with celiac disease. Prolamins from barley and/or wheat are totally or partially removed from the bulk solution during the brewing process. However, because of extensive proteolysis during fermentation, several soluble peptides that may retain or even amplify the immune-stimulating potential are released into wort following the malting and mashing steps [148]. This fact is of special relevance for the characterization and quantification of both residual proteins and neoformed peptides when quantifying the “overall” content of gluten. There is no safe beer produced from barley or wheat regarding the maximum tolerable daily intake (10 mg) for celiac disease sufferers, although depending on the grade of the disease, patients have different tolerance levels of gluten. Effectively, wheat beer (*Weissbier*) is brewed with barley and wheat, therefore is definitely incompatible with the gluten-free diet [149]. On the other hand, some brewers have developed “gluten-free” beers. If this type of beer should be considered a gluten-free product, a very low gluten product, or a product not appropriate for celiac patients, will depend on the brewing process. Brewers must be able to robustly demonstrate that they have produced a gluten-free beer. According to the Codex Alimentarius, a gluten-free food may contain about 3–20 ppm of gluten and a very low gluten product about 20–100 ppm, determined by the Enzyme-linked Immunoassay (ELISA) R5 Mendez Method. On the other hand, the FDA defines gluten-free foods as those made only from gluten-free raw materials. Several gluten-free-labeled beers contain, in fact, detectable amounts of gluten. Regular beer contains from 0 to 1542.7 mg prolamin/kg, determined by competitive ELISA [150]. Gluten concentration increases

from alcohol-free beer (<3.0 mg/L), lager beers (<3.0–8.7 mg/L), stouts (9.0–15.2 mg/L), to wheat beers (10.6–41.2 mg/L) [151].

The main problem of labeling beer (and food) for its gluten content relies on its method of quantification. Allred et al. recommended the EZ Gluten® assay as a rapid qualitative method to detect the presence of gluten in foods, but is not an appropriate method to analyze gluten for beer (or food) labeling [152]. Colgrave et al. pinpointed several problems associated with the standard ELISA methods and developed a robust and sensitive mass spectrometric method to characterize and relatively quantify a broad spectrum of hordein proteins and peptides responsible for false negatives obtained by ELISA [153]. Despite its sensitivity, and because of economical and practical reasons, the most widely used method to quantify hordeins is ELISA, which has improved sensitivity when samples are previously digested [150,151].

The brewing industry (and the food industry as well) should join the medical and scientific community in seeking a more exact definition of the peptide sequence or sequences that triggers a celiac reaction and develop methods to analyze it. Thereafter, clinical trials are warranted to demonstrate whether or not gluten-free beer can trigger a celiac auto-immune reaction in subjects with gluten intolerance.

Key points

- Beer consumption is less frequently consumed than wine in Mediterranean populations, although its consumption has been increasing over time in some of these countries. Health effects of beer are comparable to that of wine in population investigations where a typical Mediterranean diet is consumed. Thus, drinking alcohol in moderation, either as wine or beer, appears to be useful for cardiovascular protection.
- Excessive consumption and unhealthy drinking pattern (outside meals and binge) of either wine or beer is responsible for specific undesirable health effect both in Mediterranean and non-Mediterranean populations.
- Large epidemiological studies have shown that moderate (1–2 drinks/day) alcohol consumption significantly reduces cardiovascular morbidity and mortality. The dose–effect relationship is characterized by a so-called *"J-shaped curve"*.
- Epidemiological studies also suggest that regular and moderate consumption of fermented beverages (wine and beer) confer greater cardiovascular protection than spirits, possibly due to their higher phenolic content. Part of the protective effects of beer and wine is due to their alcoholic content (ethanol) and another part to their non-alcoholic components (mainly polyphenols).
- Health benefits of drinking in moderation have mainly been attributed to increase in insulin sensitivity, changes in lipid profile, increase in antioxidant capacity and decrease in systemic inflammation related to atherosclerosis, as well as to an enhanced ability to maintain endothelial integrity due to an increase in circulating endothelial progenitor cells.
- The relationship between alcohol consumption and stroke is complex, in part reflecting the heterogeneity of this vascular disease. Specific data on beer are not conclusive, although some results indicate a positive role of drinking beer in moderation against ischemic stroke. Heavy alcohol (and beer) consumption increases the risk of stroke, both ischemic and hemorrhagic.
- Heavy alcohol is strongly associated with cancers of the head and neck, esophagus and – to a lesser extent – liver, colorectal, pancreas and breast. In northern Europe, the alcohol-related cancer risk is stronger for beer than for wine or spirits. However, such an apparent excess risk is probably due to residual confounding by socioeconomic status and smoking, since (heavy) beer drinking is more common in lower social classes in those countries.
- In each population the most commonly used type of alcoholic beverage appears to be the major determinant of heavy drinking, and hence the one most strongly related to cancer risk, in the absence of material difference in risk across types of beverages.
- There is no specific cancer risk associated with beer as compared to other alcoholic beverages and, for similar level of consumption, the relative risks of cancer are similar for beer, wine and spirits.
- Excessive alcohol use is detrimental to liver function and is a major public health problem. Alcoholic beverages contain other substances that may counteract the negative effects of alcohol on the liver. Experimental studies suggest that there are substances in beer (with antioxidant properties) that may even have a positive effect on the liver.
- Epidemiological studies indicate that beer does not have a significant different relationship with mortality from liver cirrhosis than other alcoholic beverages and that the observed positive association found is mainly driven by heavy alcohol use.
- Epidemiologic studies indicate that moderate consumption of alcohol (not distinguishing among different beverages) protects against total mortality, both in healthy subjects and in cardiovascular patients. The effect is largely driven by a reduction in cardiovascular mortality. Specific data on beer are not conclusive, although some results indicate a positive role of drinking beer in moderation (1 drink/day) against total mortality. Heavy alcohol (beer) consumption increases the risk of death for any cause.
- Beer is a popular alcoholic beverage among teenagers and younger adults, whereas its appeal seems to decline with increasing age, although with considerable inter-country variations. Methodological issues and inconsistencies in assessing beer intake across surveys make international comparisons challenging. Country-specific regulations and variations in the national legal age for sales of alcohol beverages are likely to account for some of the observed differences across Europe.

- Alcohol-free beer is increasing worldwide as a non-alcoholic beverage. It can be consumed even in countries where alcohol is either wholly or partially banned, while regular (alcohol) beer consumption has to be avoided in some physiological or pathological conditions as well as for cultural or religious reasons. Alcohol-free beer contains several bioactive compounds, being a potential alternative to moderate beer consumption when alcohol consumption is banned or should be avoided.
- Gluten-free beers, which may be satisfactory for celiac individuals, are beverages with characteristics of regular beer but without its side effects induced by components rich in gluten. However, there exists a big variability in the results of gluten quantification depending on the method used, so caution should be taken when labeling a beer as gluten-free.

References

[1] Poli A, Marangoni F, Avogaro A, Barba G, Bellentani S, Bucci M, et al. Moderate alcohol use and health: a consensus document. Nutr Metab Cardiovasc Dis 2013;23:487–504.

[2] USDA National Nutrient Database for Standard Reference. Release 27. U.S. Department of Agriculture, Agricultural Research Service; 2015. http://ndb.nal.usda.gov/ndb/foods [accessed May 2015].

[3] Bendsen NT, Christensen R, Bartels EM, Kok FJ, Sierksma A, Raben A, et al. Is beer consumption related to measures of abdominal and general obesity? A systematic review and meta-analysis. Nutr Rev 2013;71:67–87.

[4] Lourenço S, Oliveira A, Lopes C. The effect of current and lifetime alcohol consumption on overall and central obesity. Eur J Clin Nutr 2012;66:813–8.

[5] Schütze M, Schulz M, Steffen A, Bergmann MM, Kroke A, Lissner L, et al. Beer consumption and the 'beer belly': scientific basis or common belief? Eur J Clin Nutr 2009;63:1143–9.

[6] Dietary reference intakes, tables and application reports. US Department of Agriculture, Agricultural Research Service; 2015. https://fnic.nal.usda.gov/dietary-guidance/dietary-reference-intakes/dri-tables-and-application-reports [accessed May 2015].

[7] Palmer C, Wolfe SH, American Dietetic Association. Position of the American Dietetic Association: the impact of fluoride on health. J Am Diet Assoc 2005;105:1620–8.

[8] Casey TR, Bamforth CW. Silicon in beer and brewing. J Sci Food Agr 2010;90:784–8.

[9] Callemien D, Collin S. Structure, organoleptic properties, quantification methods, and stability of phenolic compounds in beer – a review. Food Rev Int 2009;26:1–84.

[10] Pérez-Jiménez J, Neveu V, Vos F, Scalbert A. Identification of the 100 richest dietary sources of polyphenols: an application of the phenol-explorer database. Eur J Clin Nutr 2010;64:S112–20.

[11] González R, Ballester I, López-Posadas R, Suárez MD, Zarzuelo A, Martínez-Augustin O, et al. Effects of flavonoids and other polyphenols on inflammation. Crit Rev Food Sci Nutr 2011;51:331–62.

[12] Williamson G, Manach C. Bioavailability and bioefficacy of polyphenols in humans. II. Review of 93 intervention studies. Am J Clin Nutr 2005;81:243–55.

[13] Bonaccio M, Di Castelnuovo A, De Curtis A, Costanzo S, Persichillo M, Donati MB, et al., Moli-sani Project Investigators. Adherence to the Mediterranean diet is associated with lower platelet and leukocyte counts: results from the Moli-sani study. Blood 2014;123:3037–44.

[14] Pounis G, Bonaccio M, Di Castelnuovo A, Costanzo S, de Curtis A, Persichillo M, et al. Polyphenol intake is associated with low-grade inflammation, using a novel data analysis from the Moli-sani study. Thromb Haemost 2015;115(2).

[15] Rivero D, Perez-Magarino S, Gonzalez-Sanjose ML, Valls-Belles V, Codoner P, Muniz P. Inhibition of induced DNA oxidative damage by beers: correlation with the content of polyphenols and melanoidins. J Agr Food Chem 2005;53:3637–42.

[16] Renaud S, de Lorgeril M. Wine, alcohol, platelets, and the French paradox for coronary heart disease. Lancet 1992;339:1523–6.

[17] Costanzo S, Di Castelnuovo A, Donati MB, Iacoviello L, de Gaetano G. Wine, beer or spirit drinking in relation to fatal and non-fatal cardiovascular events: a meta-analysis. Eur J Epidemiol 2011;26:833–50.

[18] Estruch R, Sacanella E, Badia E, Antúnez E, Nicolás JM, Fernández-Solá J, et al. Different effects of red wine and gin consumption on inflammatory biomarkers of atherosclerosis: a prospective randomized crossover trial. Effects of wine on inflammatory markers. Atherosclerosis 2004;175:117–23.

[19] Sacanella E, Vázquez-Agell M, Mena MP, Antúnez E, Fernández-Solá J, Nicolás JM, et al. Down-regulation of adhesion molecules and other inflammatory biomarkers after moderate wine consumption in healthy women: a randomized trial. Am J Clin Nutr 2007;86:1463–9.

[20] Chiva-Blanch G, Magraner E, Condines X, Valderas-Martínez P, Roth I, Arranz S, et al. Effects of alcohol and polyphenols from beer on atherosclerotic biomarkers in high cardiovascular risk men: a randomized feeding trial. Nutr Metab Cardiovasc Dis 2015;25:36–45.

[21] Arranz S, Chiva-Blanch G, Valderas-Martínez P, Medina-Remón A, Lamuela-Raventós RM, Estruch R. Wine, beer, alcohol and polyphenols on cardiovascular disease and cancer. Nutrients 2012;4:759–81.

[22] Di Castelnuovo A, Costanzo S, di Giuseppe R, de Gaetano G, Iacoviello L. Alcohol consumption and cardiovascular risk: mechanisms of action and epidemiologic perspectives. Future Cardiol 2009;5:467–77.

[23] Klatsky AL. Alcohol and cardiovascular diseases: where do we stand today? J Intern Med 2015;278:238–50.

[24] Bagnardi V, Zatonski W, Scotti L, La Vecchia C, Corrao G. Does drinking pattern modify the effect of alcohol on the risk of coronary heart disease? Evidence from a meta-analysis. J Epidemiol Community Health 2008;62:615e9.

[25] Costanzo S, Di Castelnuovo A, Donati MB, Iacoviello L, de Gaetano G. Alcohol consumption and mortality in patients with cardiovascular disease: a meta-analysis. J Am Coll Cardiol 2010;55:1339–47.

[26] Mc Cambridge J, Hartwell G. Has industry funding biased studies of the protective effects of alcohol on cardiovascular disease? A preliminary investigation of prospective cohort studies. Drug Alcohol Rev 2015;34:58–66.

[27] Fernández-Solà J. Cardiovascular risks and benefits of moderate and heavy alcohol consumption. Nat Rev Cardiol 2015;12:576–87.

[28] Truelsen T, Gronbaek M, Schnohr P, Boysen G. Intake of beer, wine, and spirits and risk of stroke: the Copenhagen City Heart Study. Stroke 1998;29:2467–72.

[29] Djoussé L, Himali JJ, Beiser A, Kelly-Hayes M, Wolf PA. Apolipoprotein e, alcohol consumption, and risk of ischemic stroke: the Framingham Heart Study revisited. J Stroke Cerebrovasc Dis 2009;18:384–8.

[30] Mukamal KJ, Chung H, Jenny NS, Kuller LH, Longstreth Jr WT, Mittleman MA, et al. Alcohol use and risk of ischemic stroke among older adults: the cardiovascular health study. Stroke 2005;36:1830–4.

[31] Zhang C, Qin YY, Chen Q, Jiang H, Chen XZ, Xu CL, et al. Alcohol intake and risk of stroke: a dose–response meta-analysis of prospective studies. Int J Cardiol 2014;174:669–77.

[32] Koppes LL, Dekker JM, Hendriks HF, Bouter LM, Heine RJ. Moderate alcohol consumption lowers the risk of type 2 diabetes: a meta-analysis of prospective observational studies. Diabetes Care 2005;28:719–25.

[33] Shai I, Wainstein J, Harman-Boehm I, Raz I, Fraser D, Rudich A, et al. Glycemic effects of moderate alcohol intake among patients with type 2 diabetes: a multicenter, randomized, clinical intervention trial. Diabetes Care 2007;30:3011–6.

[34] Tresserra-Rimbau A, Rimm EB, Medina-Remón A, Martínez-González MA, López-Sabater MC, Covas MI, et al., PREDIMED Study Investigators. Polyphenol intake and mortality risk: a re-analysis of the PREDIMED trial. BMC Med 2014;12:77.

[35] Chiva-Blanch G, Arranz S, Lamuela-Raventós RM, Estruch R. Effects of wine, alcohol and polyphenols in cardiovascular risk factors: evidences from human studies. Alcohol Alcohol 2013;48:270–7.
[36] Chiva-Blanch G, Urpi-Sardá M, Ros E, Arranz S, Valderas-Martínez P, Casas R, et al. Dealcoholized red wine decreases systolic and diastolic blood pressure and increases nitric oxide: a short communication. Circ Res 2012;111:1065–8.
[37] Chiva-Blanch G, Urpi-Sarda M, Ros E, Valderas-Martinez P, Casas R, Arranz S, et al. Effects of red wine polyphenols and alcohol on glucose metabolism and the lipid profile: a randomized clinical trial. Clin Nutr 2013;32:200–6.
[38] Chiva-Blanch G, Condines X, Magraner E, Roth I, Valderas-Martínez P, Arranz S, et al. The non-alcoholic fraction of beer increases stromal cell derived factor 1 and the number of circulating endothelial progenitor cells in high cardiovascular risk subjects: a randomized clinical trial. Atherosclerosis 2014;233:518–24.
[39] Bagnardi V, Rota M, Botteri E, Tramacere I, Islami F, Fedirko V, et al. Light alcohol drinking and cancer: a meta-analysis. Ann Oncol 2013;24:301–8.
[40] Bagnardi V, Rota M, Botteri E, Tramacere I, Islami F, Fedirko V, et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose–response meta-analysis. Br J Cancer 2015;112:580–93.
[41] Praud D, Rota M, Rehm J, Shield K, Zatoński W, Hashibe M, et al. Cancer incidence and mortality attributable to alcohol consumption. Int J Cancer 2016;138:1380–7.
[42] Altieri A, Bosetti C, Talamini R, Gallus S, Franceschi S, Levi F, et al. Cessation of smoking and drinking and the risk of laryngeal cancer. Br J Cancer 2002;87:1227–9.
[43] Marron M, Boffetta P, Zhang ZF, Zaridze D, Wünsch-Filho V, Winn DM, et al. Cessation of alcohol drinking, tobacco smoking and the reversal of head and neck cancer risk. Int J Epidemiol 2010;39:182–96.
[44] La Vecchia C, Pelucchi C. Alcohol and cancer risk, with focus on moderate drinkers. Epidemiol Biostat Public Health 2015;12. http://dx.doi.org/10.2427/11209. e11209-1–e11209-3.
[45] Klatsky AL, Udaltsova N, Li Y, Baer D, Nicole Tran H, Friedman GD. Moderate alcohol intake and cancer: the role of underreporting. Cancer Causes Control 2014;25:693–9.
[46] Hashibe M, Brennan P, Chuang SC, Boccia S, Castellsague X, Chen C, et al. Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. Cancer Epidemiol Biomarkers Prev 2009;18:541–50.
[47] Hashibe M, Brennan P, Benhamou S, Castellsague X, Chen C, Curado MP, et al. Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. J Natl Cancer Inst 2007;99:777–89.
[48] Turati F, Garavello W, Tramacere I, Pelucchi C, Galeone C, Bagnardi V, et al. A meta-analysis of alcohol drinking and oral and pharyngeal cancers: results from subgroup analyses. Alcohol Alcohol 2013;48:107–18.
[49] Fedirko V, Tramacere I, Bagnardi V, Rota M, Scotti L, Islami F, et al. Alcohol drinking and colorectal cancer risk: an overall and dose-response meta-analysis of published studies. Ann Oncol 2011;22:1958–72.
[50] Lachenmeier DW, Kanteres F, Rehm J. Carcinogenicity of acetaldehyde in alcoholic beverages: risk assessment outside ethanol metabolism. Addiction 2009;104:533–50.
[51] Yoshida A, Huang IY, Ikawa M. Molecular abnormality of an inactive aldehyde dehydrogenase variant commonly found in Orientals. Proc Natl Acad Sci U S A 1984;81:258–61.
[52] Matsuo K, Rossi M, Negri E, Oze I, Hosono S, Ito H, et al. Folate, alcohol, and aldehyde dehydrogenase 2 polymorphism and the risk of oral and pharyngeal cancer in Japanese. Eur J Cancer Prev 2012;21:193–8.
[53] Gronbaek M, Becker U, Johansen D, Tonnesen H, Jensen G, Sorensen TI. Population based cohort study of the association between alcohol intake and cancer of the upper digestive tract. BMJ 1998;317:844–7.
[54] Prescott E, Gronbaek M, Becker U, Sorensen TI. Alcohol intake and the risk of lung cancer: influence of type of alcoholic beverage. Am J Epidemiol 1999;149:463–70.
[55] Bagnardi V, Rota M, Botteri E, Scotti L, Jenab M, Bellocco R, et al. Alcohol consumption and lung cancer risk in never smokers: a meta-analysis. Ann Oncol 2011;22:2631–9.
[56] La Vecchia C. Alcohol in the Mediterranean diet: assessing risks and benefits. Eur J Cancer Prev 1995;4:3–5.
[57] Bosetti C, La Vecchia C, Negri E, Franceschi S. Wine and other types of alcoholic beverages and the risk of esophageal cancer. Eur J Clin Nutr 2000;54:918–20.
[58] Altieri A, Bosetti C, Gallus S, Franceschi S, Dal Maso L, Talamini R, et al. Wine, beer and spirits and risk of oral and pharyngeal cancer: a case–control study from Italy and Switzerland. Oral Oncol 2004;40:904–9.
[59] Garavello W, Bosetti C, Gallus S, Maso LD, Negri E, Franceschi S, et al. Type of alcoholic beverage and the risk of laryngeal cancer. Eur J Cancer Prev 2006;15:69–73.
[60] Tuyns AJ, Kaaks R, Haelterman M. Colorectal cancer and the consumption of foods: a case–control study in Belgium. Nutr Cancer 1988;11:189–204.
[61] Cuzick J, Babiker AG. Pancreatic cancer, alcohol, diabetes mellitus and gall-bladder disease. Int J Cancer 1989;43:415–21.
[62] Bouchardy C, Clavel F, La Vecchia C, Raymond L, Boyle P. Alcohol, beer and cancer of the pancreas. Int J Cancer 1990;45:842–6.
[63] La Vecchia C, Negri E, Franceschi S, D'Avanzo B. Moderate beer consumption and the risk of colorectal cancer. Nutr Cancer 1993;19:303–6.
[64] Zhang C, Zhong M. Consumption of beer and colorectal cancer incidence: a meta-analysis of observational studies. Cancer Causes Control 2015;26:549–60.
[65] Gonzalez-Munoz MJ, Meseguer I, Sanchez-Reus MI, Schultz A, Olivero R, Benedi J, et al. Beer consumption reduces cerebral oxidation caused by aluminum toxicity by normalizing gene expression of tumor necrotic factor alpha and several antioxidant enzymes. Food Chem Toxicol 2008;46:1111–8.
[66] Maldonado MD, Moreno H, Calvo JR. Melatonin present in beer contributes to increase the levels of melatonin and antioxidant capacity of the human serum. Clin Nutr 2009;28:188–91.
[67] Winkler C, Wirleitner B, Schroecksnadel K, Schennach H, Fuchs D. Beer down-regulates activated peripheral blood mononuclear cells in vitro. Intern Immunopharmacol 2006;6:390–5.
[68] Ferk F, Huber WW, Filipic M, Bichler J, Haslinger E, Misík M, et al. Xanthohumol, a prenylated flavonoid contained in beer, prevents the induction of preneoplastic lesions and DNA damage in liver and colon induced by the heterocyclic aromatic amine amino-3-methyl-imidazo[4,5-f]quinoline (IQ). Mutat Res 2010;691:17–22.
[69] Sillanaukee P, van der Gaag MS, Sierksma A, Hendriks HFJ, Strid N, Ponnio M, et al. Effect of type of alcoholic beverages on carbohydrate-deficient transferrin, sialic acid, and liver enzymes. Alcohol Clin Exp Res 2003;27:57–60.
[70] Romeo J, Gonzalez-Gross M, Warnberg J, Diaz LE, Marcos A. Effects of moderate beer consumption on blood lipid profile in healthy Spanish adults. Nutr Metab Cardiovasc Dis 2008;18:365–72.
[71] Sierksma A, van der Gaag MS, Kluft C, Hendriks HF. Moderate alcohol consumption reduces plasma C-reactive protein and fibrinogen levels; a randomized, diet-controlled intervention study. Eur J Clin Nutr 2002;56:1130–6.
[72] Schmidt W, Bronetto J. Death from liver cirrhosis and specific alcoholic beverage consumption: an ecological study. Am J Public Health 1962;52:1473–82.
[73] Cohen DA, Mason K, Farley TA. Beer consumption and premature mortality in Louisiana: an ecologic analysis. J Stud Alcohol 2004;65:398–403.
[74] Narro-Robles J, Gutierrez-Avila JH. Correlacion ecologica entre consume de bebids alcoholicas y mortalidad por cirrhosis hepatica en Mexico. Salud Publica Mex 1997;39:217–20.
[75] Kerr WC, Fillmore KM, Marvy P. Beverage-specific alcohol consumption and cirrhosis mortality in a group of English-speaking beer-drinking countries. Addiction 2000;95:339–46.
[76] Renaud SC, Gueguen R, Siest G, Salamon R. Wine, beer, and mortality in middle-aged men from eastern France. Arch Intern Med 1999;159:1865–70.

[77] Becker U, Grønbæk M, Johansen D, Sørensen TI. Lower risk for alcohol-induced cirrhosis in wine drinkers. Hepatology 2002;35:868–75.
[78] Stranges S, Freudenheim JL, Muti P, Farinaro E, Russell M, Nochajski T, et al. Differential effects of alcohol drinking pattern on liver enzymes in men and women. Alcohol Clin Exp Res 2004;28:949–56.
[79] Sofi F, Macchi C, Casini A. Mediterranean diet and minimizing neurodegeneration. Curr Nutr Rep 2013;2:75–80.
[80] Collins MA, Neafsey EJ, Mukamal KJ, Gray MO, Parks DA, Das DK, et al. Alcohol in moderation, cardioprotection, and neuroprotection: epidemiological considerations and mechanistic studies. Alcohol Clin Exp Res 2009;33:206–19.
[81] Letenneur L, Larrieu S, Barberger-Gateau P. Alcohol and tobacco consumption as risk factors of dementia: a review of epidemiological studies. Biomed Pharm 2004;58:95–9.
[82] Truelsen T, Thudium D, Gronbaek M. Amount and type of alcohol and risk of dementia. The Copenhagen City Heart Study. Neurology 2002;59:1313–9.
[83] Ruitenberg A, van Swieten JC, Witteman JCM, Mehta KM, van Duijn CM, Hofman A, et al. Alcohol consumption and risk of dementia: the Rotterdam Study. Lancet 2002;359:281–6.
[84] Lindsay J, Laurin D, Verreault R, Hebert R, Helliwell B, Hill GB, et al. Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging. Am J Epidemiol 2002;156:445–53.
[85] Mukamal KJ, Kuller LH, Fitzpatrick AL, Longstreth Jr WT, Mittleman MA, Siscovick DS. Prospective study of alcohol consumption and risk of dementia in older adults. J Am Med Assoc 2003;289:1405–13.
[86] Luchsinger JA, Tang MX, Siddiqui M, Shea S, Mayeux R. Alcohol intake and risk of dementia. J Am Geriatr Soc 2004;52:540–6.
[87] Deng J, Zhou DHD, Li J, Wang J, Gao C, Chen M. A 2-year follow-up study of alcohol consumption and risk of dementia. Clin Neurol Neurosurg 2006;108:378–83.
[88] Weyrer S, Schaufele M, Wiese B, Maier W, Tebarth F, van den Bussche H, et al., for the German AgeCoDe Study Group. Age Ageing 2011;40:456–63.
[89] Di Castelnuovo A, Costanzo S, Bagnardi V, Donati MB, Iacoviello L, de Gaetano G. Alcohol dosing and total mortality in men and women: an updated meta-analysis of 34 prospective studies. Arch Intern Med 2006;166:2437–45.
[90] White IR, Altmann DR, Nanchahal K. Alcohol consumption and mortality: modelling risks for men and women at different ages. BMJ 2002;325:191.
[91] Costanzo S, Di Castelnuovo A, Donati MB, Iacoviello L, de Gaetano G. Cardiovascular and overall mortality risk in relation to alcohol consumption in patients with cardiovascular disease. Circulation 2010;121:1951–9.
[92] Wannamethee SG, Shaper AG. Type of alcoholic drink and risk of major coronary heart disease events and all-cause mortality. Am J Public Health 1999;89:685–90.
[93] Nielsen NR, Schnohr P, Jensen G, Grønbaek M. Is the relationship between type of alcohol and mortality influenced by socioeconomic status? J Intern Med 2004;255:280–8.
[94] Ferrari P, Licaj I, Muller DC, Kragh Andersen P, Johansson M, Boeing H, et al. Lifetime alcohol use and overall and cause-specific mortality in the European Prospective Investigation into Cancer and nutrition (EPIC) study. BMJ Open 2014;4:e005245.
[95] Ezzati M, Riboli E. Behavioral and dietary risk factors for noncommunicable diseases. N Engl J Med 2013;369:954–64.
[96] Athyros VG, Liberopoulos EN, Mikhailidis DP, Papageorgiou AA, Ganotakis ES, Tziomalos K, et al. Association of drinking pattern and alcohol beverage type with the prevalence of metabolic syndrome, diabetes, coronary heart disease, stroke, and peripheral arterial disease in a Mediterranean cohort. Angiology 2007;58:689–97.
[97] Naimi TS, Brewer RD, Mokdad A, Denny C, Serdula MK, Marks JS. Binge drinking among US adults. J Am Med Assoc 2003;289:70–5.
[98] Rehm J, Greenfield TK, Rogers JD. Average volume of alcohol consumption, patterns of drinking, and all-cause mortality: results from the US National Alcohol Survey. Am J Epidemiol 2001;153:64–71.
[99] Roerecke M, Rehm J. Irregular heavy drinking occasions and risk of ischemic heart disease: a systematic review and meta-analysis. Am J Epidemiol 2010;171:633–44.
[100] Rehm J, Room R, Graham K, Monteiro M, Gmel G, Sempos CT. The relationship of average volume of alcohol consumption and patterns of drinking to burden of disease: an overview. Addiction 2003;98:1209–28.
[101] European Health Interview & Health Examination Surveys Database. Brussels: Scientific Institute of Public Health (IPH); 2015. Available from: https://hishes.wiv-isp.be/index.php?hishes=home [accessed May 2015].
[102] Hibell B, Guttormsson U, Ahlström S, Balakireva O, Bjarnason T, Kokkevi A, et al. The 2011 ESPAD report-substance use among students in 36 European countries. Stockholm: The Swedish Council for Information on Alcohol and Other Drugs (CAN); 2012. Available from: http://www.espad.org/uploads/espad_reports/2011/the_2011_espad_report_full_2012_10_29.pdf [accessed May 2015].
[103] Andersson B, Hibell B, Beck F, Choquet M, Kokkevi A, Fotiou A, et al. Alcohol and drug use among European 17–18 year old students. 2007. Data from the ESPAD project. Stockholm, The Swedish Council for Information on Alcohol and Other Drugs (CAN) and the Pompidou Group at the Council of Europe. Available from: http://www.can.se/contentassets/6a22155c2e044ce0bd9b1aab79629406/espad_17-18_year_old_2003.pdf [accessed May 2015].
[104] Kuntsche E, Knibbe R, Gmel G, Engels R. 'I drink spirits to get drunk and block out my problems' beverage preference, drinking motives and alcohol use in adolescence. Alcohol Alcohol 2006;41:56–73.
[105] Alkerwi A, Sauvageot N, Françoise Donneau A, Lair ML, Couffignal S, Beissel J, et al. First nationwide survey on cardiovascular risk factors in Grand-Duchy of Luxembourg (ORISCAV-LUX). BMC Public Health 2010;10:468.
[106] Lader D, Steel M. Opinions survey report no. 42. Drinking: adults' behaviour and knowledge in 2009. NHS Information Centre, HMSO; 2009.
[107] ISTAT. La vita quotidiana nel 2009-Indagine multiscopo annuale sulle famiglie "Aspetti della vita quotidiana" Anno 2009. Roma: Istituto nazionale di statistica; 2010. Available from: http://www3.istat.it/dati/catalogo/20110121_00/inf_10_05_la_vita_quotidiana_nel_2009.pdf [accessed May 2015].
[108] Consiglio Nazionale delle Ricerche. OPGA – Osservatorio permanente sui giovani e l'alcool. Il consumo di bevande alcoliche dei giovani in Italia dal 2000 ad oggi 2015. Available from: http://www.alcol.net/images/rapporti_ricerca/brochure-alcol-v9_b.pdf [accessed September 2015].
[109] Global status report on alcohol and health. Geneva: World Health Organization; 2014.
[110] Brand DA, Saisana M, Rynn LA, Pennoni F, Lowenfels AB. Comparative analysis of alcohol control policies in 30 countries. PLoS Med 2007;4:e151.
[111] Rehm J, Rehn N, Room R, Monteiro M, Gmel G, Jernigan D, et al. The global distribution of average volume of alcohol consumption and patterns of drinking. Eur Addict Res 2003;9:147–56.
[112] Landberg J. Self-reported alcohol consumption and the risk of alcohol-related problems: a comparative risk-curve analysis of the 3 Baltic countries, Sweden, and Italy. Alcohol Clin Exp Res 2012;36:113–8.
[113] Sluik D, Bezemer R, Sierksma A, Feskens E. Alcoholic beverage preference and dietary habits: a systematic literature review. Crit Rev Food Sci Nutr 2015. http://dx.doi.org/10.1080/10408398.2013.841118.
[114] Sieri S, Krogh V, Saieva C, Grobbee DE, Bergmann M, Rohrmann S, et al. Alcohol consumption patterns, diet and body weight in 10 European countries. Eur J Clin Nutr 2009;63:S81–100.
[115] EU report The contribution made by beer in the European Economy. December 2013. Available from:, http://www.brewersofeurope.org/uploads/mycms-files/documents/archives/publications/2012/stats_2012_web.pdf [accessed September 2015].
[116] Gell L, Meier P. The nature and strength of the relationship between expenditure on alcohol and food: an analysis of adult-only households in the UK. Drug Alcohol Rev 2012;31:422–30.
[117] Johansen D, Friis K, Skovenborg E, Gronbaek M. Food buying habits of people who buy wine or beer: cross sectional study. BMJ 2006;332:519–21.

[118] Mannisto S, Uusitalo K, Roos E, Fogelholm M, Pietinen P. Alcohol beverage drinking, diet and body mass index in a cross-sectional survey. Eur J Clin Nutr 1997;51:326–32.
[119] McCann SE, Sempos C, Freudenheim JL, Muti P, Russell M, Nochajski TH, et al. Alcoholic beverage preference and characteristics of drinkers and nondrinkers in western New York (US). Nutr Metab Cardiovasc Dis 2003;13:2–11.
[120] Rouillier P, Boutron-Ruault MC, Bertrais S, Arnault N, Daudin JJ, Bacro JN, et al. Drinking patterns in french adult men – a cluster analysis of alcoholic beverages and relationship with lifestyle. Eur J Nutr 2004;43:69–76.
[121] Ruidavets JB, Bataille V, Dallongeville J, Simon C, Bingham A, Amouyel P, et al. Alcohol intake and diet in France, the prominent role of lifestyle. Eur Heart J 2004;25:1153–62.
[122] Valencia-Martin JL, Galan I, Rodriguez-Artalejo F. The association between alcohol consumption patterns and adherence to food consumption guidelines. Alcohol Clin Exp Res 2011;35:2075–81.
[123] León-Muñoz LM, Galán I, Valencia-Martín JL, López-García E, Guallar-Castillón P, Rodríguez-Artalejo F. Is a specific drinking pattern a consistent feature of the Mediterranean diet in Spain in the XXI century? Nutr Metab Cardiovasc Dis 2014;24:1074–81.
[124] Barrio-Lopez MT, Bes-Rastrollo M, Sayon-Orea C, Garcia-Lopez M, Fernandez-Montero A, Gea A, et al. Different types of alcoholic beverages and incidence of metabolic syndrome and its components in a Mediterranean cohort. Clin Nutr 2013;32:797–804.
[125] Carmen Sayon-Orea C, Bes-Rastrollo M, Nuñez-Cordoba JM, Basterra-Gortari FJ, Beunza JJ, Martinez-Gonzalez MA. Type of alcoholic beverage and incidence of overweight/obesity in a Mediterranean cohort: the SUN project. Nutrition 2011;27:802–8.
[126] Nunez-Cordoba JM, Martinez-Gonzalez MA, Bes-Rastrollo M, Toledo E, Beunza JJ, Alonso A. Alcohol consumption and the incidence of hypertension in a Mediterranean cohort: the SUN study. Rev Esp Cardiol 2009;62:633–41.
[127] May AM, Romaguera D, Travier N, Ekelund U, Bergmann MM, Kaaks R, et al. Combined impact of lifestyle factors on prospective change in body weight and waist circumference in participants of the EPIC-PANACEA study. PLoS ONE 2012;7:e50712.
[128] Bonaccio M, Di Castelnuovo A, Bonanni A, Costanzo S, De Lucia F, Pounis G, et al., Moli-sani project Investigators. Adherence to a Mediterranean diet is associated with a better health-related quality of life: a possible role of high dietary antioxidant content. BMJ Open 2013;3(8).
[129] Panico S. Commentary on alcohol use and health. Nutr Metab Cardiovasc Dis 2014;24:e25–6.
[130] Blanco CA, Andrés-Iglesias C, Monero O. Low-alcohol beers: flavour compounds, defects and improvement strategies. Crit Rev Food Sci Nutr 2014 Aug 13.
[131] Phenol-explorer: database on polyphenol content in foods. 2015. Available from: http://phenol-explorer.eu/reports/38 [accessed May 2015].
[132] Martinez N, Urpi-Sarda M, Martinez-Gonzalez MA, Andres-Lacueva C, Mitjavila MT. Dealcoholised beers reduce atherosclerosis and expression of adhesion molecules in apoE-deficient mice. Br J Nutr 2011;105:721–30.
[133] Negrão R, Costa R, Duarte D, Taveira Gomes T, Mendanha M, Moura L, et al. Angiogenesis and inflammation signaling are targets of beer polyphenols on vascular cells. J Cell Biochem 2010;111:1270–9.
[134] Vilahur G, Casani L, Guerra JM, Badimon L. Intake of fermented beverages protect against acute myocardial injury: target organ cardiac effects and vasculoprotective effects. Basic Res Cardiol 2012;107:291.
[135] Crescente M, Jessen G, Momi S, Höltje HD, Gresele P, Cerletti C, et al. Interactions of gallic acid, resveratrol, quercetin and aspirin at the platelet cyclooxygenase-1 level. Functional and modelling studies. Thromb Haemost 2009;102:336–46.
[136] Vilahur G, Casani L, Mendieta G, Lamuela-Raventos RM, Estruch R, Badimon L. Beer elicits vasculoprotective effects through Akt/eNOS activation. Eur J Clin Invest 2014;44:1177–88.
[137] Asahara T, Murohara T, Sullivan A, Silver M, van der Zee R, Li T, et al. Isolation of putative progenitor endothelial cells for angiogenesis. Science 1997;275:964–7.
[138] Martinez Alvarez JR, Belles VV, Lopez-Jaen AB, Marin AV, Codoner-Franch P. Effects of alcohol-free beer on lipid profile and parameters of oxidative stress and inflammation in elderly women. Nutrition 2009;25:182–7.
[139] Nothlings U, Murphy SP, Wilkens LR, Henderson BE, Kolonel LN. Flavonols and pancreatic cancer risk: the multiethnic cohort study. Am J Epidemiol 2007;166:924–31.
[140] Liu M, Hansen PE, Wang G, Qiu L, Dong J, Yin H, et al. Pharmacological profile of xanthohumol, a prenylated flavonoid from hops (*Humulus lupulus*). Molecules 2015;20:754–79.
[141] Gerhauser C, Alt A, Heiss E, Gamal-Eldeen A, Klimo K, Knauft J, et al. Cancer chemopreventive activity of Xanthohumol, a natural product derived from hop. Mol Cancer Ther 2002;1:959–69.
[142] Busch C, Noor S, Leischner C, Burkard M, Lauer UM, Venturelli S. Anti-proliferative activity of hop-derived prenylflavonoids against human cancer cell lines. Wien Med Wochenschr 2015;165:258–61.
[143] Schneider C, Thierauf A, Kempf J, Auwarter V. Ethanol concentration in breast milk after the consumption of non-alcoholic beer. Breastfeed Med 2013;8:291–3.
[144] Rewers M. Epidemiology of celiac disease: what are the prevalence, incidence, and progression of celiac disease? Gastroenterology 2005;128(4 Suppl 1):S47–51.
[145] Fasano A, Catassi C. Current approaches to diagnosis and treatment of celiac disease: an evolving spectrum. Gastroenterology 2001;120:636–51.
[146] Ludvigsson JF, Leffler DA, Bai JC, Biagi F, Fasano A, Green PH, et al. The Oslo definitions for coeliac disease and related terms. Gut 2013;62:43–52.
[147] Pulido OM, Gillespie Z, Zarkadas M, Dubois S, Vavasour E, Rashid M, et al. Introduction of oats in the diet of individuals with celiac disease: a systematic review. Adv Food Nutr Res 2009;57:235–85.
[148] Sollid LM. Coeliac disease: dissecting a complex inflammatory disorder. Nat Rev Immunol 2002;2:647–55.
[149] Picariello G, Mamone G, Cutignano A, Fontana A, Zurlo L, Addeo F, et al. Proteomics, peptidomics, and immunogenic potential of wheat beer (Weissbier). J Agric Food Chem 2015;63:3579–86.
[150] Haas-Lauterbach S, Immer U, Richter M, Koehler P. Gluten fragment detection with a competitive ELISA. J AOAC Int 2012;95:377–81.
[151] Dostalek P, Hochel I, Mendez E, Hernando A, Gabrovska D. Immunochemical determination of gluten in malts and beers. Food Addit Contam 2006;2006(23):1074–8.
[152] Allred LK, Park ESEZ. Gluten for the qualitative detection of gluten in foods, beverages, and environmental surfaces. J AOAC Int 2012;95:1106–17.
[153] Colgrave ML, Goswami H, Blundell M, Howitt CA, Tanner GJ. Using mass spectrometry to detect hydrolysed gluten in beer that is responsible for false negatives by ELISA. J Chromatogr A 2014;1370:105–14.