REVIEW

Moderate alcohol use and health: A consensus document

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A. Poli [a,*], F. Marangoni [a], A. Avogaro [b], G. Barba [c],
S. Bellentani [d], M. Bucci [e], R. Cambieri [f], A.L. Catapano [g],
S. Costanzo [h], C. Cricelli [i], G. de Gaetano [j],
A. Di Castelnuovo [k], P. Faggiano [l], F. Fattirolli [m], L. Fontana [n], G. Forlani [o],
S. Frattini [p], R. Giacco [q], C. La Vecchia [r], L. Lazzaretto [s], L. Loffredo [t],
L. Lucchin [u], G. Marelli [v], W. Marrocco [s], S. Minisola [w], M. Musicco [x], S. Novo [y],
C. Nozzoli [z], C. Pelucchi [r], L. Perri [t], F. Pieralli [z], D. Rizzoni [aa], R. Sterzi [ab],
R. Vettor [ac], F. Violi [t], F. Visioli [ad]

[a] NFI (Nutrition Foundation of Italy), Viale Tunisia 38, 20124 Milan, Italy
[b] SIPREC (Italian Society for Cardiovascular Prevention) and University of Padova, Italy
[c] SIIA (Italian Society of Hypertension), Institute of Food Science — Italian National Research Council — CNR, Avellino, Italy
[d] Gastroenterology and Liver Center, Local Health Agency of Modena, "Ramazzini" Hospital, Carpi, Italy
[e] SISA (Italian Society for the Study of Atherosclerosis) and Clinical Research Center Ce.S.I. "Università G. d'Annunzio" Foundation, University of Chieti, Italy
[f] SNAMID (National Society of Medical Education), Milan, Italy
[g] SITECS (Italian Society for Clinical and Experimental Therapy) and Department of Pharmacology and Biomolecular Sciences, University of Milan, Italy
[h] Laboratory of Genetic and Environmental Epidemiology, Catholic University, Campobasso, Italy
[i] SIMG (Italian Society of General Medicine), Florence, Italy
[j] Research Laboratories, "John Paul II" Foundation for Research and Treatment, Catholic University, Campobasso, Italy
[k] Laboratory of Genetic and Environmental Epidemiology, "John Paul II" Foundation for Research and Treatment, Catholic University, Campobasso, Italy
[l] ANMCO (Italian National Association of Hospital Cardiologists) and Chair of Cardiology, University of Brescia, Italy
[m] ANMCO (Italian National Association of Hospital Cardiologists), Careggi Hospital and University of Florence, Italy
[n] AMD (Italian Association of Diabetologists), Dietology, Diabetology and Metabolic Diseases Unit, Sandro Pertini Hospital, Rome, Italy
[o] AMD (Italian Association of Diabetologists), Unit of Metabolic Diseases & Clinical Dietetics Alma Mater Studiorum, University of Bologna, Italy
[p] ANMCO (Italian National Association of Hospital Cardiologist) and Cardiology Unit — Istituti Ospitalieri di Cremona, Italy
[q] SID (Italian Society of Diabetology) and Institute of Food Science — National Research Council-CNR, Avellino, Italy
[r] "Mario Negri" Pharmacological Research Institute and Department of Clinical Sciences and Community Health, University of Milan, Italy

* Corresponding author.
  E-mail address: poli@nutrition-foundation.it (A. Poli).

ˢ FIMMG (Italian Federation of General Medicine Doctors), Rome, Italy
ᵗ SIMI (Italian Society of Internal Medicine), Department of Internal Medicine and Medical Specialties, University of Rome "La Sapienza", Italy
ᵘ ADI (Italian Association of Dietetics), Dietetics and Clinical Nutrition Unit, Bolzano Health District, Bolzano, Italy
ᵛ AMD (Italian Association of Diabetologists), Diabetology and Metabolic Diseases Unit, Desio and Vimercate Hospital, Italy
ʷ SIOMMMS (Italian Society of Osteoporosis Mineral Metabolism and Skeletal Diseases), Department of Internal Medicine and Medical Disciplines, University of Rome "Sapienza", Italy
ˣ CNR-ITB (Institute of Biomedical Technologies of the National Research Council), Milan, Italy
ʸ SIC (Italian Society of Cardiology), Chair of Cardiovascular Diseases, Department of Biomedicine, Internal and Specialities (DIBIMIS), University of Palermo, Italy
ᶻ FADOI (Italian Federation of the Associations of Internal Medicine Physicians), University Hospital Careggi, Florence, Italy
ᵃᵃ SIIA (Italian Society of Hypertension), Department of Clinical and Experimental Sciences, University of Brescia, Italy
ᵃᵇ The Italian Stroke Forum, Azienda Ospedaliera Niguarda Cà Granda, Milan, Italy
ᵃᶜ SIO (Italian Society of Obesity), Department of Medical and Surgical Sciences, Azienda Ospedaliera-University of Padova, Italy
ᵃᵈ Laboratory of Functional Foods, Madrid Institute for Advanced Studies (IMDEA) − Food, CEI UAM + CSIC, Madrid, Spain

Abstract *Aims:* The aim of this consensus paper is to review the available evidence on the association between moderate alcohol use, health and disease and to provide a working document to the scientific and health professional communities.

Data synthesis: In healthy adults and in the elderly, spontaneous consumption of alcoholic beverages within 30 g ethanol/d for men and 15 g/d for women is to be considered acceptable and do not deserve intervention by the primary care physician or the health professional in charge. Patients with increased risk for specific diseases, for example, women with familiar history of breast cancer, or subjects with familiar history of early cardiovascular disease, or cardiovascular patients should discuss with their physician their drinking habits. No abstainer should be advised to drink for health reasons. Alcohol use must be discouraged in specific physiological or personal situations or in selected age classes (children and adolescents, pregnant and lactating women and recovering alcoholics). Moreover, the possible interactions between alcohol and acute or chronic drug use must be discussed with the primary care physician.

Conclusions: The choice to consume alcohol should be based on individual considerations, taking into account the influence on health and diet, the risk of alcoholism and abuse, the effect on behaviour and other factors that may vary with age and lifestyle. Moderation in drinking and development of an associated lifestyle culture should be fostered.

Alcoholic beverages are being consumed for millennia: humans drink them for pleasure, for their energy content or for behavioural and ritual reasons. Starting from the second half of the last century, an increasing number of studies — mostly epidemiological in nature — carefully examined the associations between consumption of alcohol and human health. The general view, at that time, was that, while excessive alcohol consumption is noxious and clearly associated with increased incidence of disease, moderate consumption might be associated with reduced cardiovascular risk. Further studies associated moderate consumption of alcohol with reduced incidence also of metabolic and neurodegenerative diseases. Conversely, a positive association has been reported with increased risk of developing some neoplasias. The World Health Organization (WHO) has a 'zero tolerance' policy on alcohol consumption, but an intense scientific debate is currently taking place to confirm or dispute such an approach.

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Methodology

The Nutrition Foundation of Italy coordinated a team of Italian experts, as follows: selected Italian scientific societies were contacted and required to provide topic-specific reviews of the alcohol−health relation. Twenty societies out of 23 agreed (see Appendix 1), although one finally chose not to contribute to this document. All contributions were

merged, discussed and agreed upon by the entire Panel, which approved the final paper in September 2012.

Methodological limitations in the assessment of alcohol—health associations

All studies on the associations between alcohol and health are methodologically complex. This is due to the methods used to assess alcohol consumption, to the choice of control groups and to the correct definition of confounding factors. Assessment of alcohol consumption is usually done by specific questionnaires, where frequency and amount of consumption are collected. This procedure often underestimates the true rate of consumption, especially in heavy drinkers, who tend to report lower-than-habitual use [1]. Such evaluation bias raises some interpretation issues: a) when excessive alcohol consumption is found to have untoward effects, these are attributed to intakes that are lower than that inducing the effects and b) concerning healthy effects attributed to moderate alcohol consumption, an underestimation of 'optimal' intake and of the minimal levels at which the benefits would disappear, will be computed [2].

Because the alcohol—health association not only depends on quantities but also on patterns of alcohol use (in other words, whether intakes are concentrated on times such as the weekends or are regularly spread during weekly meals), it is also important to clearly take such patterns into account in addition to the mere quantities [1,2]

The selection of control groups is crucial in studies that associate alcohol and health. Usually, abstainers are chosen as the reference group, whereas drinkers are classified based on levels of intake. However, the group of 'abstainers' often includes subjects who report rare though not nil consumption. Given that such subjects may under-report their intakes, the contribution of their inclusion among the controls to the overall effect might not be negligible [3]. Former drinkers too are often included in the teetotallers' group. Notably, those who quit drinking often do so because of health reasons. The inclusion of these subjects in control groups might place the latter at a false higher risk level ('sick-quitter hypothesis') [4]. Therefore, ex-drinkers should only be included in *ad-hoc* categories. Moderate consumption of alcoholic beverages has often been associated with healthier lifestyles and higher socio-economic status (though with cigarette smoking too) [5]. These associations might explain, at least in part, the apparent reduced risk of cardiovascular disease (CVD) and overall mortality in moderate drinkers vs. teetotallers [4]. In any event, these important confounding factors should be carefully taken into account when performing or analysing association studies [3,4].

Another caveat in statements on alcohol and health is related to the current absence of randomised clinical trials. Indeed, all currently available data are based on observational studies. While randomised clinical trials would eventually contribute to better clarify the role of alcohol in human health, such studies are obviously very difficult to perform for both practical and ethical reasons [3,4,6].

In summary, epidemiological analyses of the association between alcohol and health are complex and require keen attention to the various confounders, bias, and methodological issues that might lead to unsound conclusions.

Alcohol and CVD disease

Coronary heart disease and fatal arrhythmia

Data derived from epidemiological studies and obtained in primary care individuals consistently show the existence of a significant inverse association between moderate alcohol use and cardiovascular risk (mainly, myocardial infarction and stroke). Conversely, excessive intake does increase cardiovascular risk. Several meta-analyses reported a 'J'-shaped curve that describes the association between alcohol consumption and cardiovascular risk, namely a higher risk associated to both abstention and excessive intakes as compared with moderate consumption. The maximal reduction of cardiovascular risk (fatal and non-fatal events) associated with moderate consumption has been estimated to be approximately 30%.

In some studies, actually, the inverse association between alcohol use and infarction risk reduction appeared to be linear, that is increasing alcohol consumption correlated with a continually decreasing risk. Such association was observed, as an example, in the Health Professional cohort [5], in which maximum protection was observed in consumers of 50 g or more of alcohol, that is four drinks[1] per day. A recent meta-analysis [7] reported a "J" association in women but not in men, in whom higher levels of intake were associated with lower coronary risk. In this meta-analysis, the protective effect was seen in all age groups, even though risk reduction — in absolute terms — increased with age. In the most recent meta-analysis by Ronksley et al. [8], consumption of alcoholic beverages was associated with a 25—50% reduction of fatal and non-fatal coronary event risk as compared with teetotallers. Low-to-moderate alcohol consumption was associated with a reduction of cardiovascular and all-cause risk reduction also in a cohort of 14,125 hypertensive men selected from the Physicians' Health Study [9]; a further analysis of the same cohort reported an inverse association between moderate alcohol use and incidence of coronary heart disease (CHD). In this analysis, risk reduction was 40% in subjects who drank more than eight drinks/week.

In diabetic subjects a meta-analysis of six prospective studies evidenced a close association between moderate alcohol consumption and reduced coronary disease; the reduction of relative risk (RR) was similar in magnitude to that seen in the general population and in hypertensive patients [10].

Less evidence is presently available to describe the effects of alcohol in patients with pre-existing CHD [11,12]. A recent meta-analysis of eight studies involving a total of 16,531 subjects with cardiovascular events reported that a low-to-moderate (5—25 g/d) alcohol consumption is associated with a significantly lower incidence of cardiovascular

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[1] By definition, one drink is a standard ~150 ml wine glass, or a can of beer, or a standard shot glass ~40 ml of liquor. This standard drink contains ~12 g of ethanol.

and all-cause mortality. These data confirm in CHD patients what has been observed in healthy subjects. A positive effect of moderate alcohol consumption was also apparent in patients who underwent angioplasty procedures, in whom both atherosclerosis progression and clinical relapses appeared to be positively influenced by alcohol intake [6,13].

In the area of secondary prevention, one aspect that deserves attention is the possible interaction between alcohol and pharmacological therapy. In particular, close attention should be paid to the interaction between alcohol and anti-platelet drugs or oral anticoagulants, which can increase the risk of haemorrhages.

As far as arrhythmias are concerned, binge drinking has been associated with increased risk of atrial fibrillation, that is, the so-called 'holiday heart syndrome'. Recently, it was suggested that even the habitual intake of high alcohol doses (35 drinks/week or more) might correlate with arrhythmia risk [14—16]. A recent meta-analysis indicated a linear, dose—response association between alcohol use and risk of atrial fibrillation [17]. These data suggest that the risk of arrhythmia proportionally increases with daily doses of alcohol; presumably, a reduction of alcohol consumption or even abstinence would be associated with lower atrial fibrillation risk. Conversely, sudden death due to ventricular arrhythmias was reportedly less frequent in both men and women who consumed approximately one drink/d [18,19].

In summary, as far as primary prevention is concerned, moderate alcohol use by apparently healthy individuals is associated with significant reduction of cardiovascular risk and sudden death due to ventricular arrhythmias. The presence of risk factors such as hypertension does not seem to markedly modify this association. Patients with pre-existing CVD could get similar benefits from moderate alcohol consumption but should pay attention to the possible interaction of alcohol with their pharmacological regimen. Excessive alcohol consumption is specifically dangerous for patients with cardiomyopathy or supraventricular arrhythmias, being able to worsen their arrhythmic risk.

Stroke

Several prospective studies evaluated the association between alcohol consumption and risk of stroke. Most studies reported a 'J'-shaped association, especially concerning ischaemic strokes; because of the relatively low incidence of haemorrhagic stroke, the effects of alcohol on total strokes are similar to those observed for ischaemic strokes.

A meta-analysis of both cohort and case—control studies [20] reported a 'J'-shaped association between alcohol consumption and total and ischaemic stroke risk, while a linear positive association was observed between alcohol intake and haemorrhagic stroke. In particular, subjects who consumed <12 g or between 12 and 24 g/d of alcohol, that is one to two drinks/d were attributed a significantly reduced risk as compared with teetotallers (RR = 0.80 and 0.72, respectively). Higher alcohol consumption, that is more than 60 g, or five drinks/d was conversely associated with a significant increase of both ischaemic (RR = 1.69) and haemorrhagic (RR = 2.18) strokes. A more recent

meta-analysis [21] confirmed these data, which were not modified following adjustment for cerebrovascular mortality and morbidity. Finally, the most recent meta-analysis on this topic [8] — which pooled a sample of hundreds of thousands of individuals — indicates that stroke risk reduction (both as mortality and incidence) is significant only in association with a daily alcohol intake between 2.5 and 14.9 g (RR = 0.86 and 0.80, respectively).

In the Reynolds et al. meta-analysis [20], stroke RR as associated with alcohol intake was also analysed for sex. Even though the 'J'-shaped curve was seen in both sexes, stroke RR for consumptions >60 g, that is five drinks/d was higher in women than in men (RR = 4.29 and 1.76 vs. abstainers, respectively). The fact that women appear to be more sensitive to the effects of high intakes was confirmed by Ronksley et al. [8], who specifically analysed haemorrhagic stroke. However, the Nurses' Health Study (NHS) — maybe because of the limited number of subjects who consumed elevated alcohol quantities — did not report such an untoward effect [22].

Few studies separately analysed the role played by different alcoholic beverages on stroke risk. The results of the Stroke Prevention in Young Women Study [23] suggest that wine exerts protective effects that were not recorded for either beer or liquor. In a meta-analysis of the effects of alcohol on cerebrovascular diseases [24], a stratified analysis also suggested protective effects of wine, but not of beer, consumption. Conversely, no significant difference was observed among the various kinds of beverages within the Framingham [25] and the Northern Manhattan Studies [26].

Data on the protective effects of moderate alcohol consumption are corroborated by the EPIC Norfolk (Norfolk cohort of European Prospective Investigation of Cancer study), where more than 20,000 subjects were followed up for over a decade. This study underscored the interaction between alcohol consumption and 'healthy' lifestyles that include abstinence from smoking, appropriate diet and physical exercise. These four features halved stroke risk as compared with people who did not follow such guidelines. The adoption of one to three of these indications reduced risk to a significantly lower extent [27].

The results of the Physician's Health Study suggest that low-to-moderate alcohol consumption and stroke-risk reduction are also associated in secondary prevention [28]. Patients who drank in moderation exhibited lower cardiovascular mortality (though not specifically for stroke) as compared with non-drinkers. It must be underlined that risk evaluation should be exerted with great care on individual bases. A recent study [29] suggests that the protective effects of moderate alcohol intake on stroke risk can be significantly attenuated in the presence of high serum concentrations of gamma-glutamyltransferase (gamma-GT), which postulates an inadequate estimate of alcohol consumption or concomitant diseases that would reduce any beneficial effect.

Binge drinking [30] is usually associated with more elevated stroke risk, possibly because of the increase in blood pressure that follows large alcohol intakes [31]. Accordingly, increased risk within the first two hours of alcohol assumption has been reported at all levels of consumption [32]. Apparently, this phenomenon is transitory and, within 24 h, risk ratios return to 'habitual' values.

In summary, moderate consumption is associated with reduced risk of total stroke and notably of ischaemic events; conversely, consumption of elevated quantities of alcohol is an important risk factor for any type of stroke.

Peripheral artery disease

Several pieces of evidence, as discussed above [24,33,34], support an inverse association between alcohol use and acute CVD risk; conversely, the risk of developing non-acute atherosclerotic diseases in relation to alcohol use has been poorly investigated. Among such disorders, peripheral artery disease (PAD) has a high prevalence and concerns >5% of subjects older than 60 years [35]; PAD itself is considered as a main cause of disability. Indeed, PAD patients are exposed to complications that may lead to amputation and experience an increased incidence of cardiovascular events such as myocardial infarction, ischaemic stroke and cardiovascular death. Therefore, PAD can be considered a marker of systemic atherosclerosis and its early diagnosis might be useful in identifying patients at high cardiovascular risk. The evidence of a link between alcohol intake and PAD is modest if compared with that relative to coronary or cerebrovascular disorders (see above). Among the studies that took such a possible association into consideration, both the Strong Heart Study [36] and the Rotterdam Study [37] reported an inverse association between moderate alcohol use and PAD diagnosis (based on reduced Winsor indices). Such an association appears to be stronger in women than in men, even though another study reported the converse [38]. A subsequent sub-analysis of one of the two studies mentioned above, which examined PAD progression, recorded an inverse association between alcohol consumption and variation at 5 years of the Winsor index [39].

Two prospective studies evaluated the association between alcohol use and PAD risk in the general population. In an analysis from the Framingham Heart Study [40], which selected symptomatic PAD as the 'end' point, the authors reported a hazard ratio of 0.67 associated with a consumption of 13—24 g/d, that is, one to two drinks/d for men and of 0.44 associated with a consumption of 7—12 g/d, that is, one half to one drink/d for women. In the Physicians' Health Study, Camargo et al. [41] reported a hazard ratio of 0.74 associated with a consumption of seven or more drinks/week; the analysis, on the other hand, included only 66 PAD cases. In the latter study, alcohol use was associated with a 26% risk reduction of *claudicatio intermittens*. Another study, however, carried out in a diabetes mellitus cohort did not report any association between alcohol consumption and PAD [42]. Although PAD risk reduction was associated with preferential consumption of wine or beer in the Framingham Study [40], or with wine consumption in a sub-analysis of the Edinburgh Artery Study [38], the majority of studies failed to attribute the observed reduced risk of developing PAD to any particular alcoholic beverage.

Finally, a limited number of studies evaluated the association between moderate alcohol use and risk of developing abdominal aorta aneurysms (AAAs). An analysis of male smokers reported a 'U'-shaped association curve between alcohol intake and AAA risk, with RR reductions ranging from 0.74 for consumptions up to 15 g/d to 0.60 for intakes up to 30 g/d and increased risk for higher intakes [43].

In summary, the association between moderate alcohol consumption and extra-coronary CVD is complex and heterogeneous. In particular, epidemiological studies confirm that PAD risk is reduced by moderate alcohol intake, that is, in the one to two drinks/d range. However, larger prospective studies are necessary to more precisely define the association between alcohol use and peripheral vascular disorders and to formulate recommendations.

Alcohol and cardiovascular risk factors

Lipid profile

An early review, published in 1999 [44], suggested that moderate alcohol use is associated with increased plasma concentrations of high-density lipoprotein (HDL) cholesterol (HDL-c), with a clear dose—response relationship, namely, an increase of 0.133 mg/dl for every gram of alcohol ingested daily. Likewise, every gram of alcohol was associated with a 0.294 mg/dl increase in plasma apolipoprotein A-I levels (Apo-AI; the foremost component of HDL) and of 0.190 mg/dl in triacylglycerol (TG) plasma levels. Total cholesterolaemia was not influenced by alcohol intake, while TG increase was more obvious in the post-prandial phase.

Alcohol consumption would induce increased hepatic synthesis of Apo-AI, Apo-AII and of HDL-C and its subfractions HDL_1, HDL_2 and, notably, HDL_3 via increased activity of lipoprotein lipase (LPL) [45]. Alcohol might also influence the activity of other key metabolic enzymes such as lecithin:cholesterol acyl-transferase (LCAT) and cholesterol-ester-transfer protein (CETP). In particular, alcohol increases LCAT activity while decreasing CETP, in turn increasing HDL-c concentrations and reverse cholesterol transport [46].

It remains however to be established whether alcohol-induced increase of HDL-c concentrations would entirely explain its cardioprotective properties. Indeed, on the one hand intervention studies failed to show that increasing HDL-c lowers cardiovascular mortality [47]; on the other, HDL exerts a number of cardioprotective actions including reduced low-density lipoprotein (LDL) oxidation, inhibition of inflammatory molecules migration into the sub-endothelial space and reverse cholesterol transport [48].

In summary, moderate alcohol use dose-dependently increases HDL-c and Apo-AI (see also a recent meta-analysis by Brien et al.[49]). Conversely, no significant alterations of total and LDL-c are observed. Increased TGs usually occur after the ingestion of >60 g/d, that is, five drinks/d of alcohol only. These overall favourable effects might contribute to the reduction of cardiovascular risk observed in moderate alcohol drinkers.

Blood pressure

The effects of alcohol on blood pressure are manifold. Only modest intakes appear to be healthful; usually, a linear association between alcohol intake and increased blood pressure is reported in both normal subjects and

hypertensive patients [50,51]. The hypertensive effect of alcohol, in interventional studies, is yet reversible [51]

Several observational studies suggested that intake of alcohol in excess increases blood pressure [52]. Klatsky et al. evaluated blood-pressure changes as related to alcohol use in 83,947 men and women and concluded that those who consumed >3 drinks/d had higher systolic and diastolic pressure values as compared with teetotallers [53]. In 1995, Gillman et al. reported — in young adults — a 'J'-shaped association between alcohol use and blood pressure, minimal values being noted in those who consumed one or two drinks/d [54]. A simple linear association was, in contrast, reported by others [55]. Compulsive drinkers exhibit higher risk for stroke in the early morning, which has been tentatively linked to a possible circadian effect of alcohol on blood pressure [56]. Consumption of several drinks in the evening appears to induce a moderate increase in daytime pressure but a reduction in the night-time one. The net effect is that of a mild overall increase, at least in Japanese subjects [57]. Normotensive subjects from the Women's Health Study and Physicians' Health Study cohorts have been examined to ascertain the risk of developing hypertension in relation with alcohol consumption. This analysis concerned 28,848 healthy women and 13,455 healthy men. The results show a decreased risk of incident hypertension in drinking women, but an increased risk in men as compared with abstainers. Consumption threshold, apparently, is four drinks a day for women vs. just one drink for men [58]. Some authors observed that acute alcohol ingestion was associated with a sudden drop in blood pressure (because of either direct or indirect vasodilatory effects), followed by an increase [59].

Genetic polymorphisms of enzymes that metabolise alcohol, for example aldehyde dehydroxygenase, might influence their effects on blood pressure [60].

The mechanism(s) by which ethanol influences blood pressure have not been clarified yet. While alcohol itself might stimulate the production of endothelin ET-1, whose urinary excretion is in fact increased by alcoholic beverages [51], red wine polyphenols might reduce its synthesis by inhibition of ET1 gene transcription [61]. Endothelial function might also augment after red wine ingestion [62—64], possibly independent from an effect of alcohol *per se* [63]. However, *ad-hoc* clinical studies measuring flow-mediated dilation yielded mixed results [65].

In summary, available data suggest that alcohol in very moderate amounts appears to exert neutral or beneficial effects on blood pressure and that red wine might be superior to other alcoholic beverages [24,66,67]. Because moderate alcohol use is being associated with better cardiovascular prognosis in hypertensive patients, consumption levels of <30 g/d, that is 2.5 drinks/d for men and <15 g/d, that is ~one drink/d for women, though hypertensive, might be advantageous over abstention [57].

Inflammation and circulating surrogate markers of CVD

Several epidemiological studies reported an association between moderate alcohol intake and low plasma concentrations of inflammation markers (Table 1). A study carried

Table 1 Effects of moderate alcohol consumption on the main markers of inflammation and on hemostasis factors in epidemiological and intervention studies.

	Epidemiological studies	Intervention studies
C-reactive protein (CRP)	+++	+/−
Interleukin-6 (IL-6)	+	+/−
Tumour necrosis factor-α (TNF-α)	+/−	+/−
Fibrinogen	++	+++
Plasminogen activator inhibitor-1 (PAI-1)	+/−	+/−
Tissue plasminogen activator (TPA)	+/−	+/−
Adiponectin	+	++

Effects: +/− uncertain; + modest; ++ strong; +++ very strong.

out on two large cohorts, that is men from the Health Professionals Follow-up Study, HPFS, and women from the Nurses' Health Study II, NHSII, reported that, in comparison to abstainers, 15—30 g/d alcohol consumption was associated with a reduction in serum concentrations of C-reactive protein (CRP), interleukin 6 (IL-6) and the soluble tumour necrosis factor-alpha (TNF-alpha) receptors, sTNF-R1 and sTNF-R2 [68]. Men who consumed one or two drinks/d had 26% CRP and 36% IL-6 lower concentrations than teetotallers. Women exhibited a similar trend at half of the intake levels of men [68]. Similar results have also been reported by Imhof et al. [69], who showed a 'U'-shaped relationship between serum CRP concentration and alcohol intake. In particular, lower serum CRP levels were observed at 20—40 g/d alcohol intake, while higher concentrations were found at ≥80 g/d alcohol intake [69]. The purported anti-inflammatory effect of alcohol intake up to 40 g/d has been confirmed in many European populations, in which lower serum fibrinogen and leucocyte concentrations and decreased haematic viscosity have been found to be associated with reduced CRP levels in moderate drinkers, regardless of the kind of drink [70]. Other studies, for example the Health, Aging and Body Composition Study, investigated the association between IL-6 and alcohol consumption, thus highlighting a 'J'-shaped curve, with the nadir placed at one-to-seven drinks/week [71]. A similar pattern has also been observed for CRP, but not for TNF-alpha and plasminogen activator inhibitor-1 (PAI-1). In addition in diabetic patients, moderate alcohol intake is associated with lower serum concentrations of fibrinogen, sTNF-R2 and soluble vascular adhesion molecule-1 (sVCAM-1) as well as higher levels of adiponectin [72].

Although methodological differences in alcohol-intake assessment impair conclusive results, the overall body of evidence seems to suggest an anti-inflammatory effect of restrained alcohol consumption. However, the 'J'- and 'U'-shaped curves mentioned above are indicative of a threshold value over which alcohol intake may have a pro-inflammatory effect.

The few intervention studies that investigated the effects of moderate alcohol consumption on circulating

concentrations of PCR, IL-6, TNF-alpha, PAI-1 and tissue plasminogen activator (TPA) yielded conflicting results (Table 1). A recent meta-analysis showed that low alcohol intake reduces serum concentrations of PCR, IL-6 and TNF-alpha, although to a non-significant extent [49]. This meta-analysis only included five studies on CRP, three on TNF-alpha and two on IL-6. Conversely, alcohol consumption significantly increases adiponectin (four studies) and decreases fibrinogen (seven studies) by an average of 0.20 g/l, which might contribute to its hypothesised cardio-protective effects [73]. As far as adiponectin is concerned, the effects of alcohol are unclear and data are scant. Moderate alcohol consumption increases adiponectin concentrations by 0.6 mg/L on average [74], that is, an increase similar to that produced by the powerful insulin-sensitisers thiazolinediones [75].

The effects of alcohol on other haemostatic parameters such as plasminogen, thromboxane, von Willebrand's factor and E-selectin as well as those on endothelial markers, for example intracellular adhesion molecule 1 (ICAM) and VCAM are still unclear as data are insufficient and conflicting.

Metabolic effects of alcohol

Metabolic syndrome

The metabolic syndrome (MS) is a multifactorial disorder that, according to the recent International Diabetes Federation definition, requires the presence of central obesity and at least two of the four following abnormalities: high TGs, low HDL-c, high blood pressure or raised fasting plasma glucose level. According to the Adult Treatment Panel-III (ATP-III) definition (with which the general practitioner is more familiar), the presence of any three of the five risk factors mentioned above allows to diagnose the MS [76].

The relation between alcohol intake and MS prevalence is controversial, as alcohol has positive effects on some of its factors, for example HDL-c serum concentrations and negative effects on other ones, for example blood pressure levels [77].

Observational studies from different geographic areas report reduced MS prevalence in moderate drinkers and an increase of MS prevalence in abstainers, heavy drinkers and those who started to drink early in their lives. Therefore the relation between alcohol consumption and MS risk is 'J'- or 'U'-shaped. Freiberg et al. [78] observed in low-to-moderate drinkers a reduced MS prevalence of 48% in men and 47% in women younger than 50, regardless of ethnic origin, in comparison to abstainers. This study, which individually evaluated separately the various components of the MS, suggested that moderate alcohol consumption was associated with reduced prevalence of low serum concentration of HDL-c, high levels of TG and higher waist circumference, as well as hyperinsulinaemia [78]. This association was stronger in consumers of wine and beer, while liquor drinkers showed only a favourable association with HDL-c levels. However, other studies do not confirm the positive association between moderate alcohol consumption and MS risk. For instance, a study carried out in Italy, performed on subjects between 65 and 84 years of age, reported that moderate alcohol intake significantly worsened, in men but not in women, three out of the five components of MS, that is systolic blood pressure, glycaemia and waist circumference, suggesting a sex effect of ethanol [79].

Indeed, a recent meta-analysis that also took into account sex, showed that ethanol intake of <40 g/d, that is ~3.5 drinks/d in men and <20 g/d, that is ~ two drinks/d in women reduces the risk of MS by 16% and 25%, respectively, as compared with abstainers (Table 2) [80].

Alcohol and insulin sensitivity

The beneficial effects of moderate alcohol consumption on the MS and some of its components have been attributed to an amelioration of insulin sensitivity, partly mediated by lower visceral adiposity. This effect, observed in several epidemiological studies, has not been conclusively confirmed by intervention studies that, being devoid of confounders, are the most suitable for clarifying potential mechanisms of action.

In observational studies, alcohol consumption of 10—30 g/d, that is ~ one or two drinks/d is associated with lower fasting insulin concentrations and lower markers of insulin resistance, under both fasting and glucose load conditions [81,82]. In particular, the Normative Aging Study [81] showed that the relation between alcohol intake and insulin sensitivity markers is not linear, as consumers of one to two drinks/d were less insulin-resistant than subjects who consumed either less or more than this amount. On the contrary, no association between alcohol, insulin sensitivity (as evaluated by euglycaemic clamp) and insulin secretion was reported by the Uppsala Longitudinal Study of Adult Men

Table 2 Relative risk of metabolic syndrome as related to the habitual alcohol consumption of men and women: a meta-analysis of seven observational studies.

Alcohol consumption	Category 1 0—39.9 g/d	Category 2 40—59.9 g/d	Category 3 >60 g/d
Men	RR (95% CI): 0.84 (0.75, 0.94) $P = 0.004$	RR (95% CI): 0.95 (0.83, 1.09) $P = 0.49$	OR (95% CI): 0.99 (0.71, 1.38) $P = 0.94$
Women	Category 1 0—19.9 g/d	Category 2 20—39.9 g/d	
	RR (95% CI): 0.75 (0.64, 0.89) $P = 0.0007$	RR (95% CI): 0.81 (0.57, 1.14) $P = 0.22$	—

RR, Relative Risk; CI, Confidence Interval. Modified from Alkerwi A et al. [80]. Note that consumption levels used for computation are different between men and women.

[83]. An inverse relation between moderate alcohol consumption and insulin resistance has been reported in normal-weight subjects, but not in overweight/obese patients with a Homeostasis Model of Assessment (HOMA) index <2 [84].

The few available intervention studies provide controversial results. However, the majority of them indicates that 25–39 g/d ethanol consumption, that is ~ two or three drinks/d improves lipid profile and insulin sensitivity as well as serum adiponectin in menopausal women [85,86], while in men it seems to have no influence on insulin sensitivity and fat distribution and, indeed, it may promote hepatic steatosis [74,87].

In summary, epidemiological data support a reduction of MS risk associated with low-to-moderate alcohol consumption. This effect is particularly evident for some of the MS components such as HDL-c and fasting insulin levels. However, due to the limited sample size and short duration (3–8 weeks), the few intervention studies do not allow ascertaining the role of ethanol intake on insulin sensitivity.

Alcohol, overweight and obesity

The addition of alcohol to a normocaloric diet should increase body weight because of the added calories. Moreover, alcohol increases appetite (due to its hypoglycaemic action) and facilitates socialisation, in turn increasing food intake [88]. However, observational studies failed to correlate alcohol use with body weight. In an American women cohort, Wannamethee et al. [89] observed that the lowest body mass index (BMI) values were associated with alcohol intakes of 5–30 g/d; in a 13-year follow-up, moderate alcohol use was also associated with lower chance to gain weight or to become overweight or obese [90]. Likewise, the National Health and Nutrition Examination Survey (NNAHES) cohort exhibited a clear inverse association between moderate alcohol intake and obesity risk (and, to a lower extent, overweight risk) [91]. In particular, total and abdominal adipose tissue in moderate drinkers is reportedly less than that in abstainers or heavy drinkers [92], even if an intervention study on 35–70-year-old men failed to observe any variation of abdominal fat following the consumption of 40 g d^{-1} for 4 weeks [74].

In summary, the association between alcohol use and body weight is multifaceted and difficult to correctly compute, mostly because of the many confounding factors that hamper its correct assessment. However, while elevated alcohol intake is associated with increased risk of obesity or overweight, moderate consumption appears to have neutral or favourable effects [93].

Alcohol and diabetes

Alcohol consumption has always been considered a risk factor for diabetes mellitus. However, recent publications suggest that moderate alcohol use might actually be associated with reduced incidence of type 2 diabetes mellitus (T2DM) and its vascular complications.

A meta-analysis by Koppes et al., which analysed 15 studies on 369,862 patients followed up for an average of 12 years, concluded that subjects who consumed 6–48 g/d, that is one-half to four drinks/d of ethanol exhibited a 30% reduced risk of

T2DM as compared with teetotallers or consumers of >48 g/d of ethanol [94]. This effect is independent of either sex or BMI. In addition, a lower incidence of T2DM was observed in women with moderate alcohol intake (but not in men) when compared with abstainers in a prospective study by Hodge et al. [95] Moderate alcohol use and reduction of cardiovascular risk in diabetic patients are also associated [96].

Moderate alcohol consumption and cardiovascular risk in diabetics have also been found to be inversely associated in the Second Manifestations of ARTerial (SMART) disease study [97]: moderate (10–20 drinks/week) ethanol use was associated with reduced risk of acute coronary disease and stroke (hazard ratio (HR) 0.39; confidence interval (CI): 0.20–0.76) as well as lower overall mortality (HR 0.40; CI 0.24–0.69), when compared with abstainers. This association was also apparent when red wine was highlighted.

Recently, Djousse et al. [98], based on the results of an investigation on 28,345 women, concluded that the positive association between moderate alcohol use and cardiovascular risk reduction can be partly explained by the beneficial effects of ethanol on glucose metabolism, in addition to lipid profile, inflammation and blood pressure.

Current guidelines addressed to diabetic patients are rather cautious because of the calories and body-weight issues, in addition to some untoward metabolic and vascular effects of alcohol. In brief, such guidelines indicate that if a diabetic adult chooses to drink alcohol, his/her daily intake should be kept constantly modest (10–13 g, i.e., one drink or less for women and 20–25 g, i.e., two drinks/d or less for men). To reduce the risk of nocturnal hypoglycaemia in patients on insulin or insulin secretagogues, alcohol should be ingested with food [99].

Moderate alcohol use and liver disease

Alcoholic liver disease (ALD) is the most prevalent cause of advanced liver disease in the Western world. It comprises a large spectrum of liver injuries, ranging from fatty liver or simple steatosis (alcoholic fatty liver disease, AFLD) to acute alcoholic hepatitis, alcoholic steatohepatitis (ASH), chronic hepatitis with hepatic fibrosis and cirrhosis [100,101]. Non-alcoholic fatty liver disease (NAFLD), on the other hand, is the most common liver disorder in Western countries and affects as many as 25–30% of adults. NAFLD might shortly become the most common liver disease worldwide [102].

The distinction between NAFLD and AFLD or between NASH (non-alcoholic steatohepatitis) and ASH is based on average daily alcohol consumption, the discriminating threshold being 20–30 g/d [102] by international standards. Therefore, proper diagnosis is based on daily alcohol-intake determination. In clinical practise, this is usually done by estimating the 'drinks per day' consumption (see above in this paper for the definition of drink units) [103].

In the general population, the daily threshold of alcohol intake associated with an increased risk of liver injury is between one and two drinks per day for women and two and three drinks per day for men. Certainly, drinkers of more than 30–50 g/d of alcohol for more than 5–10 years are exposed to a significant risk to develop ALD. Not all these drinkers, however, develop a liver disease. Indeed, we know that some

host- and environment-related predisposing factors promote ALD development [100,101]. For example, genetic polymorphisms of alcohol dehydrogenase and their interaction with genes involved in the generation and scavenging of free radicals influence susceptibility to ALD [100]. Obesity, diabetes, insulin resistance, metabolic syndrome (including NAFLD) as well as hepatitis C virus (HCV) infection increase the liver-damaging effects of alcohol [100,101].

Current belief is that low or moderate alcohol consumption should be forbidden in patients with liver disease. Therefore, subjects with chronic liver disease (regardless of its aetiology), are usually warned by clinicians to avoid any kind of alcoholic beverage. Conversely, whether moderate, that is less than one to two units per day, that is 20—30 g/d daily alcohol intake could be safe in patients with NAFLD remains an open issue.

Only 4—5% of patients with NAFLD, namely those exhibiting a more severe subtype known as steatohepatitis (NASH, which is characterised by inflammatory infiltrates, ballooning hepatocellular injury and fibrosis) are at a high risk for cirrhosis- and hepatocellular carcinoma (HCC)-related mortality. We also know that most non-cirrhotic NAFLD patients who are moderate drinkers are not at significant risk of worsening their liver disease [104—107]. Patients with NAFLD and, especially, those with NASH, are — conversely — at increased risk for cardiovascular or coronary-heart disease (CVD or CHD). Indeed, they are twice more likely to die from CVD than from liver diseases [108]. Evaluation of cardiovascular risk and management of CHD risk factors is, therefore, mandatory in these patients.

As moderate alcohol use not only is associated with reduced CHD morbidity and mortality risk, but also improves metabolic risk factors related to both CVD and NAFLD [85,109] and seems to partially protect from NASH and NAFLD [106,107], patients with NAFLD who drink no more than two-three drinks per day could perhaps be allowed to continue their drinking habits. This issue is, however, still unresolved [110].

Alcohol, cognitive impairment and dementia

Five epidemiological studies have been published on the association between alcohol use and incidence of dementia and Alzheimer's disease [111—115]. In addition, two meta-analyses examined 26 and 15 studies, respectively [116,117].

The available evidence comes mostly from longitudinal cohort studies, in which non-dement or mild cognitive impairment (MCI) elderly have been followed to monitor their cognitive performance. The results are summarised in Table 3.

All studies revealed a reduction of dementias and Alzheimer's risk associated with moderate alcohol use, as compared with abstainers. The extent of risk reduction greatly varies among studies and meta-analyses. All studies reported a negative association between alcohol intake and risk of dementia; publication bias is unlikely, but cannot be ruled out. Alcohol would decrease cerebrovascular risk via one or more mechanisms described above, such as its anti-inflammatory effect [118]. This is supported by a recent study showing that ethanol is able to reduce the synaptic damage induced by beta-amyloid and synuclein [119]. One should not forget however that alcohol in excess causes at least two well-known neurological diseases characterised by cognitive decline and dementia, that is Wernicke—Korsakoff's and Marchiafava—Bignami's syndromes, and that an alcohol-mediated form of dementia has been described, which is accompanied by cerebral atrophy and a typical alteration of white and grey matters.

Alcohol, skeletal frailty and osteoporosis

Several observational studies indicate that alcohol consumption might influence bone density, depending on intake levels. In general, moderate alcohol use has no significant influence on bone density (or it has even positive effects), whereas data on heavy intake are conflicting, mainly pointing to negative effects on bone structure.

The effects of two or three drinks/d depend on age, sex and hormonal profile; for example positive effects are described for menopausal, but not for fertile women. The type of alcoholic beverage might also be important, as favourable effects have also been reported separately for wine [120] and beer [121]. These observations might be explained by the non-alcoholic content of either beverage. In a human study [122], consumption of two drinks/d increased bone density, while more than two glasses/d exerted detrimental effects on both spine and femur. Finally, in a study carried out in twins with different alcohol use, moderate consumption was associated with higher bone mass [123]. A very recent and large study in postmenopausal women observed that the association between moderate consumption and higher bone mass cannot be explained by lifestyle, hence suggesting some direct effect of ethanol [121].

As far as mechanisms of action are concerned, alcohol has been suggested to slow bone resorption with no effects on bone formation; in turn, the net consequence on mass would be positive [124]. This hypothesis is partly confirmed by the observation that low-to-moderate alcohol use, that is <27 drinks/week for men and <13 drinks/week for women has not been associated with any increased fracture risk [125,126].

One note of caution concerns the deleterious effects of high alcohol intake. Indeed, excessive and prolonged alcohol consumption lowers bone density and is considered a major risk factor for bone fractures [125,127].

Alcohol and cancer

Most cancers are reportedly not associated with moderate alcohol intake. Only the association between light alcohol consumption and cancer risk for sites for which sufficient or limited evidence for carcinogenicity of alcohol is available [128,129], that is, cancers of the upper digestive and respiratory tract (oral and pharyngeal cancer, oesophageal squamous cell carcinoma and laryngeal cancer), colorectum, pancreas and breast will be examined in this paper. Adenocarcinoma of the oesophagus will not examined because this neoplasm is not to be associated to alcohol drinking [130].

A positive association between alcohol and liver cancer has been established [128]. However, the latter will not

Table 3 Original studies and meta-analyses of the associations between alcohol intake and dementia and/or cognitive decline.

Title	Characteristics and No. participants	Outcome (cases)	Alcohol consumption	Relative risk estimate (95% CI)
Alcohol consumption and risk of dementia: the Rotterdam Study [111].	Cohort population study on 7893 non-demented subjects	Dementia (197) AD (146)	1—3 drinks/d vs. nondrinkers	0·58 (0·38—0·90)
Alcohol consumption and cognitive function in late life: a longitudinal community study [113].	Cohort study on 1098 non-demented elderlies	Reduction cognitive test or neurocognitive tests	Minimal and moderate drinker vs. nondrinker	For any increase of one SD in the reduction of MMSE the risk of being minimal drinker vs. that of an abstainer was 0.3 (0.14—0.65) and 0.08 (0.02—0.28) that of moderate drinkers
Alcohol intake and risk of dementia [112]	Cohort study on 980 non-demented elderlies	Dementia (260) AD (199)	Three vs. zero servings of wine	0.55 (0.84—0.39)
Current alcohol consumption and its relationship to incident dementia [115]	Cohort study on 3202 non-demented elderlies (≥75 years)	Dementia (217) AD (111)	Any kind of alcohol intake vs. no intake	0.71 (0.53—0.96) dementia 0.58 (0.38—0.89) AD
Alcohol consumption, mild cognitive impairment, and progression to dementia [114]	Cohort study on 121 MCI subjects	Dementia (14)	<1 drink/d vs. no intake	0.15 (0.03—0.78)
Alcohol, dementia and cognitive decline in the elderly: a systematic review [116]	Meta-analysis of 26 cohort and case—control studies	Dementia and cognitive decline	Small amounts of alcohol intake	0.63 (0.53—0.75) dementia 0.57 (0.44—0.74) AD
Alcohol consumption as a risk factor for dementia and cognitive decline: meta-analysis of prospective studies [117]	Meta-analysis of 15 cohort studies	Dementia, VAD, AD	Light to moderate intake vs. no intake	0.74 (0.61—0.91) dementia 0.75 (0.57—0.98) VAD 0.72 (0.61—0.86) AD

AD, Alzheimer's disease; VAD, Vascular dementia; MCI, Mild cognitive impairment; MMSE, Mini Mental Status Examination; CI, Confidence Interval.

be analysed here because of known problems in the interpretation of results from epidemiological, mainly case—control, studies. In fact, most alcohol-related liver cancers follow cirrhosis, which leads to a reduction of alcohol drinking and, thus, to a substantial underestimation of the real associations [131]. Therefore, quantification of risks for low-to-moderate alcohol consumption and liver cancer remains unresolved. Alcohol drinking might be inversely associated to kidney cancer and non-Hodgkin lymphoma [128]. These issues, however, will not be discussed here.

Establishing if there is or not any positive association between low doses of alcohol and some cancers known to be alcohol-related is particularly important [132], as it is still unclear whether there is an alcohol threshold below which alcohol drinking would not affect cancer development.

Figure 1 shows the main results for light alcohol drinking, defined as one or few drinks/d, from meta-analyses of studies on selected digestive tract and larynx cancers [133—137]. Summary data on light drinking and breast cancer risk were extracted from the collaborative re-analysis of 53 epidemiological studies of breast cancer [138] and from the Million Women Study [139].

For oral and pharyngeal cancer, two meta-analyses, based on 19 case—control studies and one cohort study, provided evidence that an increased risk is present also at low doses of alcohol consumption [136,140] (overall RR 1.21 (95% CI, 1.10—1.33) for one or few drinks/d vs. Non-/occasional drinkers) [136]. The corresponding estimates were 1.17 (95% CI, 1.01—1.35, based on nine studies) for oral cavity and 1.23 (95% CI, 0.87—1.73, based on five studies) for pharyngeal cancers [140]. The sensitivity analyses provided no evidence for a substantial influence of studies reporting estimates unadjusted for smoking.

A meta-analysis of oesophageal squamous cell carcinoma reported an association with low doses of alcohol similar to that of oral and pharyngeal cancer [134]. The summary RRs for light drinking were 1.31 (95% CI, 1.10—1.57) for the overall analysis, based on 26 studies and 1.35 (95% CI, 0.92—1.98) for cohort studies alone (8 studies). When the analysis was stratified by geographical area, the association was stronger in Asia (RR = 1.63; 95% CI, 1.20—2.22) than in other regions of

the world (RR = 1.17; 95% CI, 0.99—1.39), suggesting a potential effect modification by environmental or genetic susceptibility. No increase in risk by consumption of low doses of alcohol was observed in never-smokers (RR = 0.74; 95% CI, 0.47—1.16), but the estimate was based on five studies only.

By contrast, laryngeal cancer was not associated with alcohol consumption up to one drink/d [135]. The summary RR for light drinking, based on 10 case—control and two prospective studies, was 0.88 (95% CI, 0.71—1.08). Results were unaffected by several subgroup analyses, including that adjusted for smoking.

Almost 50 studies provided information on low doses of alcohol and colorectal cancer risk [133]. No overall association was reported with either colorectal (RR = 1.00; 95% CI, 0.95—1.05), or colon (RR = 0.96; 95% CI, 0.90—1.02) or rectal (RR = 1.06; 95% CI, 0.98—1.14) cancers. Results were consistent across strata of sex, geographical area and various other covariates.

A meta-analysis on alcohol and pancreatic cancer found strong evidence supporting the lack of positive associations at low-to-moderate alcohol intakes defined as less than three drinks/d [137]. Seventeen case—control and seven cohort studies were included and the summary RR was 0.92 (95% CI, 0.86—0.97). The estimates were almost the same when case—control or prospective studies were considered separately. When the analyses were repeated comparing consumption of one or less drink/d to non-occasional drinkers, the odds ratio (OR) was 0.91 (95% CI, 0.86—0.98). Similarly, in the PanScan study [141], the pooled OR was, if anything, higher in non-drinkers (OR = 1.19; 95% CI, 0.97—1.48) as compared with drinkers of less than 5 g d^{-1} of alcohol; also, there was no clear association up to consumption of <30 g d^{-1}.

In a collaborative meta-analysis on breast cancer [138], the RRs were 1.01 (p > 0.05) for women reporting alcohol consumption <5 g/d and 1.03 (p > 0.05) for those consuming 5—14 g/d, as compared with women who did not drink. The Million Women Study [139] found RRs of 1.00 (p > 0.05) for ≤2 drinks/week, that is, <3 g/d of alcohol and 1.08 (p < 0.05) for 3—6 drinks/week, that is, around 4—8 g/d, compared with non-drinkers. Exclusive consumption of wine showed a similar risk pattern. Thus, results for breast cancer are not totally consistent, but indicate a small increase in risk even for light drinking, in the order of one drink/d. This finding may have different impact on women according to their menopausal state: indeed, in young women, especially those with familiar history of cancer, even a small increase of breast cancer risk by moderate alcohol consumption would be unacceptable because it would not be counterbalanced by a concomitant positive effect on a very low cardiovascular risk. In contrast, a small increase of breast cancer risk by moderate alcohol use in post-menopausal women would appear negligible with respect to the substantial reduction of a high cardiovascular risk.

In summary, moderate drinking of up to one drink/d leads to an increased risk of 20—30% of oral and pharyngeal cancer and of oesophageal squamous cell carcinoma, though these estimates remain open to discussion due to under-reporting. No significant association emerges with the risk of laryngeal, colorectal and pancreatic cancers. An increased risk of breast cancer appears at intakes of three to six drinks/week. A positive association between alcohol and liver cancer has been established, but no reliable quantification of the risks for low-to-moderate alcohol consumption is as yet possible.
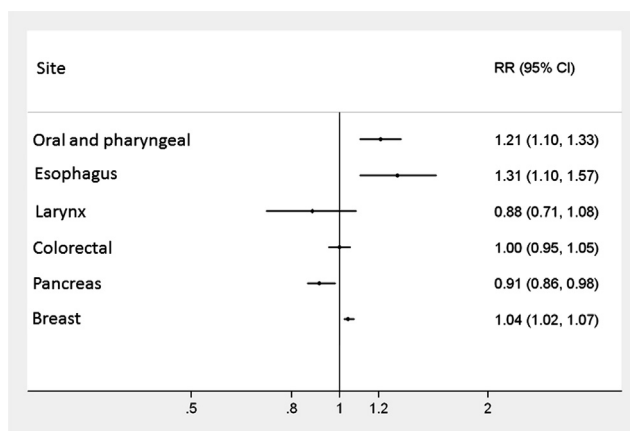

Site	RR (95% CI)
Oral and pharyngeal	1.21 (1.10, 1.33)
Esophagus	1.31 (1.10, 1.57)
Larynx	0.88 (0.71, 1.08)
Colorectal	1.00 (0.95, 1.05)
Pancreas	0.91 (0.86, 0.98)
Breast	1.04 (1.02, 1.07)

Figure 1   Moderate alcohol use and cancer risk in selected sites. RR, relative risk for alcohol intakes of ≤1 drink/d, as compared with abstainers and occasional drinkers.

In terms of attributable fraction of cancers that would be eliminated by restricting alcohol consumption, about 390,000 (3.6%) cancers and 230,000 (3.5%) cancer deaths were attributed in 2002 to worldwide alcohol drinking [142]. These included over 5% of cancers and cancer deaths in men and about 1.5% of cancers and cancer deaths in women. Restriction of alcohol drinking to the limits indicated by the European Code Against Cancer [143] (20 g/d for men and 10 g/d for women) would avoid about 90% of cancers and cancer deaths in men and over 50% of cancers in women, that is about 330/360,000 cancer cases and about 200/220,000 cancer deaths (Bagnardi et al., 2012). Avoidance or limitation of alcohol consumption to two drinks/d for men and one drink/d for women is, therefore, a global public-health priority.

Alcohol and all-cause mortality

The most objective way to evaluate the role of alcohol in health is to assess total mortality (i.e., for all causes) associated with its use. Infarction, risks and benefits are, in this manner, compared with the same epidemiological hard 'end' point.

The association between total mortality and alcohol consumption not only depends on quantities and drinking behaviour, but also on the distribution of causes of death in the population at study. Further to the first study that showed a 'J'-shaped association between alcohol use and all-cause mortality [144], a meta-analysis combined the results of 34 prospective studies and investigated the association between alcohol consumption and all-cause mortality in over 1 million apparently healthy subjects. The results indicate that alcohol intake up to 40 g/d was inversely associated with reduction of all-cause mortality, a maximum effect being apparent at about 6 g of ethanol per day. More than 3—4 drinks/d, conversely, were associated with a progressive linear increase in overall mortality [3]. This meta-analysis also separately analysed men and women [3]; maximal theoretical protection was similar in both sexes (mean reduction ~18%, at about 6 g/d, i.e., half a drink/d). The 'reversion point', that is the dose of alcohol associated with the same mortality as that observed in the

control group of abstainers, was reached at 1—1.5 drinks/d in women and at about 3 drinks/d in men (Fig. 2). Clinical and biochemical data suggest that, indeed, women are more prone to the noxious effects of alcohol than men.

Another meta-analysis of seven prospective studies of 12,553 cardiovascular (acute myocardial infarction, stroke, or coronary disease) patients confirmed the risk reduction associated with moderate alcohol use, with a maximal significant decrease by 18% associated with 5—10 g/d of ethanol, which is maintained up to 26 g/d [12]. Even though we do not currently have enough data on secondary prevention in women, it is conceivable that their 'allowed' dose be similar to that of healthy women [145,146]. On the contrary, alcoholic patients with previous myocardial infarction exhibit a risk level for all-cause mortality that is double than that of regular and moderate drinkers [16]. Patients with CVD who drink >3 drinks/d should be warned of the risk of haemorrhage associated with alcohol abuse concomitant with acetylsalicylic-based drugs [145]

Also in the elderly, moderate alcohol use is associated with reduced all-cause death. In a study of 2000 subjects between 55 and 65 years of age at enrolment and followed up for an average of 20 years, total mortality was halved — after 15 years — in moderate drinkers as compared with teetotallers [147].

Starting from the second half of the 1990s, several epidemiological studies have documented the existence of a 'J'-shaped curve that describes the association of alcohol use (and abuse) and total mortality. This curve also indicates a 'window' of consumption that might be incorporated into healthy lifestyles. Likewise, heavy drinking should be firmly discouraged.

Differential health effects of the various alcoholic beverages

Alcoholic beverages contain both ethanol and other components. The quality and quantity of the latter differs greatly between wine, beer and spirits, as well as within these categories (red vs. white wine, different beers, etc.). While the role of ethanol in human health has been elucidated to a great extent, that of the non-alcoholic components is less clear. Several experimental studies (in vitro and in animals) suggest that these components (in particular, polyphenols) might play important protective roles in human health [148,149]. Therefore, it has been hypothesised that polyphenol-rich alcoholic beverages such as red wine might be superior, in terms of healthy effects, to polyphenol-poor beverages. Particular attention has been paid to resveratrol, to which several of the alleged healthy effects of wine have been attributed, even though no human data are available [150]. Indeed, red wine contains not only resveratrol but phenols, tannins and flavonoids such as catechins and quercetin [151]. Some experimental evidence suggests that these components are endowed with healthful characteristics [152], such as antioxidant, anti-thrombotic and anti-inflammatory properties. As plaque formation is partially due to the oxidation of LDL within the arterial wall, polyphenols might retard this process and reduce atheroma formation [153]. Polyphenols such as resveratrol and quercetin inhibit platelet function and
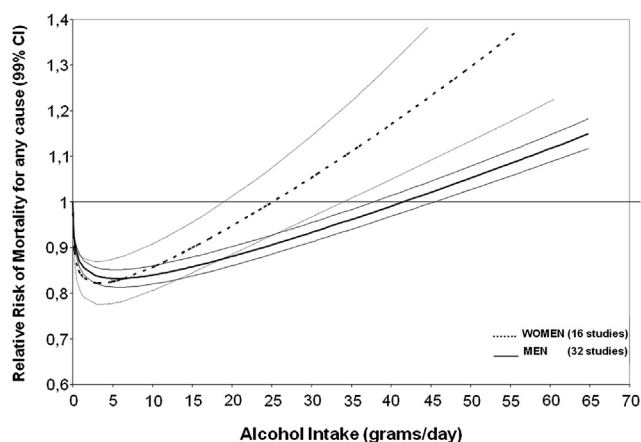

Figure 2 Relative risk of all-cause mortality and alcohol consumption in men and women. Data are from Di Castelnuovo et al. 2006 [3].

tissue factor, in turn reducing plaque formation. These effects are independent of the intake of anti-platelet drugs such as aspirin [154]. *In vitro*, resveratrol interferes with the formation of inflammatory mediators by leucocytes, reduces thrombogenicity linked to adhesion molecules and prevents thrombosis in animals via nitric oxide formation [155]. Wine consumption too has been associated with decreased concentrations of inflammatory markers such as CRP and higher levels of long-chain omega-3 fatty acids [156]. Notably, red wine is the alcoholic beverage richest in polyphenols (though it contains resveratrol only in small amounts), but beer and some spirits also contain marked quantities of these compounds [150]. Indeed, polyphenols from wine and beer have been suggested to positively affect CVD, diabetes, some cancers, cognitive decline, Alzheimer's disease and respiratory tract disorders [150,157].

Even though data from basic research consistently suggest favourable biological effects of polyphenols, epidemiological evidence in support of these effects in humans is scant [4,150,157,158]. As an example, the potential differences between wine and beer, as far as cardiovascular pathology and total mortality are concerned, have been recently compared by a meta-analysis that involved over 280,000 subjects [159]. The conclusion indicates that the effects of wine and beer do not differ significantly, reiterating the hypothesis that ethanol plays a major cardioprotective role [159] regardless of the polyphenolic content of the various beverages. No comparative data on wine vs. beer and spirits are available on total mortality, nor do we have enough evidence to say that red wine exerts effects different from that of white wine [24,159]. Concerning other pathological conditions, epidemiological data comparing wine and beer are scant and inconclusive [4,150,157,158]. Some authors believe that the type of alcoholic beverage determining the strongest event reduction in a particular country is the one most consumed locally [160].

In conclusion, the hypothesis that the antioxidant and anti-inflammatory properties of non-alcoholic components might determine health effects different from that of ethanol is intriguing, but — at present — only suggested by laboratory data but not by conclusive epidemiological evidence.

Conclusions

Dozens of epidemiological studies and the meta-analyses that analysed their results clearly show a statistically significant association between moderate alcohol consumption, that is two or three drinks/d or 24—36 g of ethanol/d for men and one to two drinks/d or 12—24 g of ethanol/d for women and risk reduction of specific clinical events, namely those involving the cardio-circulatory system such as atherosclerosis, myocardial infarction or ischaemic (though not haemorrhagic) stroke. This association — which concerns both primary and secondary prevention — appears to be largely independent of confounding factors, as the inclusion of 'sick quitters' in the control groups of abstainers or the socioeconomic status of the cohorts. In population studies, the incidence of other common pathological conditions such as T2DM, dementia and osteoporosis also appears to be positively influenced by moderate alcohol use.

Moderate alcohol use appears on the other hand to be associated with modest but significant increased risk of cancers of the upper respiratory and gastrointestinal tracts, as well as of breast cancer.

The association between ethanol intake and all-cause mortality — which computes the overall effects on different diseases — follows the well-known 'J'-shaped curve: mortality among moderate drinkers is significantly lower than that of teetotallers and that of heavy drinkers. The nadir of this curve is located at consumption levels of approximately one drink/d; the mortality rate reverts to the levels of abstainers at consumption of 40 g/d in men and 20—25 g/d in women. Above these levels, overall mortality exceeds that of teetotallers.

The available data, namely the time sequence between exposure and effects, the dose—response association and the biological plausibility of the effects, suggest that the observed effects of alcohol are likely to be causal. In particular, moderate alcohol use favourably influences known risk factors for CVD such as plasma levels of HDL-c, fibrinogen, CRP, etc. These systemic effects might indeed explain the association between intake levels and cardiovascular risk reduction. Available data strongly suggest that it is ethanol rather that some other non-alcoholic component that exerts the proposed protective effects, even though an additive effect of, for example, polyphenols cannot be ruled out and is plausible. Moreover, the protective effects of alcohol only appear if its consumption is moderate and regular over time. Binge drinking, for example on limited occasions such as the weekends, is not associated with any positive effect and should be strongly discouraged. This caveat also applies to those who need to drive automobiles or use dangerous equipment.

The bulk of available data allows proposing some suggestions and guidelines, addressed to physicians and health professionals:

1) In adults and in the elderly (regardless of sex), spontaneous consumption of alcoholic beverages within 30 g ethanol/d, that is ~two drinks/d for men and 15 g/d, that is ~one drink/d for women are to be considered acceptable and do not deserve intervention by the primary care physician or the health professional in charge. In fact, there is no evidence to suggest complete abstention from alcohol drinking by moderate users.
2) Patients with increased risk for specific diseases, for example women with familiar history of breast cancer, or subjects with familiar history of early CVD or cardiovascular patients should discuss their drinking habits with their physician.
3) No abstainer should be advised to drink for health reasons.
4) Alcohol use must be discouraged in specific physiological or personal situations or in selected age classes (children and adolescents, pregnant and lactating women and recovering alcoholics). Moreover, the possible interactions between alcohol and acute or chronic drug use must be discussed with the primary care physician.

Disclosure to the lay public of the available notions between moderate alcohol use and health is debated and calls for caution. We propose that experts accurately communicate the health benefits and risks of alcohol consumption to the media and to the public, based on our current understanding and available evidence. In particular, the 'J'-curve, demonstrating potential health benefits of low-to-moderate alcohol consumption and increased risk for degenerative disease (mainly beginning at the fourth decade of life)

associated with abstinence or excessive consumption, including the concentrated use of alcohol over short periods (binge drinking), needs to be judiciously and carefully explained.

The choice to consume alcohol should be based on individual considerations, taking into account the influence on health and diet, the risk of alcoholism and abuse, the effect on behaviour and other factors that may vary with age and lifestyle.

Moderation in drinking and development of an associated lifestyle culture should be fostered.

Appendix 1. Scientific societies that have agreed to sign the consensus paper

ADI (Associazione Italiana di Dietetica e Nutrizione Clinica)
AMD (Associazione Medici Diabetologia)
ANMCO (Associazione Nazionale Medici Cardiologi Ospedalieri)
CNR-ITB (Istituto di Tecnologie Biomediche del Centro Nazionale della Ricerca)
FADOI (Italian Federation of the Associations of Internal Medicine Physicians)
FIMMG (Federazione Italiana Medici Medicina Generale)
NFI (Nutrition Foundation of Italy)
SIC (Società Italiana di Cardiologia)
SID (Italian Society of Diabetology)
SIIA (Società Italiana dell'Ipertensione Arteriosa)
SIMG (Società Italiana di Medicina Italiana)
SIMI (Società Italiana Medicina Interna)
SIO (Società Italiana dell'Obesità)
SIOMMMS (Società Italiana dell'Osteoporosi del Metabolismo Minerale e delle Malattie dello Scheletro)
SIPREC (Società Italiana per la Prevenzione Cardiovascolare)
SISA (Società Italiana per lo Studio della Arteriosclerosi)
SITECS (Società Italiana Terapia Clinica e Sperimentale)
SNAMID (Società Nazionale di Aggiornamento per il Medico di Medicina Generale)
The Italian Stroke Forum

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