Nutrition and Aging 2 (2014) 101–109
DOI 10.3233/NUA-140039
IOS Press

Wine, alcohol, polyphenols and cardiovascular disease

R. Estruch[a,b,*] and R.M. Lamuela-Raventós[b,c]

[a]*Department of Internal Medicine, Hospital Clinic, Institut d'Investigacions Biomédiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Barcelona, Spain*
[b]*CIBEROBN Fisiopatologia de la Obesidad y la Nutrición and RETIC RD06/0045 Alimentación saludable en la prevención primaria de enfermedades crónicas: la Red Predimed. Instituto de Salud Carlos III, Spain*
[c]*Nutrition and Food Science Department, CeRTA, INSA Pharmacy School, University of Barcelona, Barcelona, Spain*

Abstract. Excessive alcohol consumption is associated with increased morbidity and mortality as well as with labour and traffic accidents. However, current evidence suggests beneficial effects of moderate drinking on cardiovascular events including coronary heart disease, ischaemic stroke, peripheral arterial disease and congestive heart failure. The underlying mechanisms to explain these protective effects against coronary heart disease include an increase in high-density lipoprotein cholesterol and an increase in insulin sensitivity, and a decrease in platelet aggregation and circulating concentrations of fibrinogen. However, there are discrepancies regarding the specific effects of different types of beverages on the cardiovascular system, and also whether the possible protective effects of alcoholic beverages are due to their alcohol component (ethanol) or non-alcoholic products containing, mainly polyphenols. Recent randomised clinical trials have shown that wine, a polyphenol-rich alcoholic beverage, provides higher antioxidant and anti-inflammatory effects than some spirits such as gin, a polyphenol-free alcoholic beverage. In addition, dealcoholized red wine decreases blood pressure through a nitric oxide mediated mechanism, suggesting a protective effect of polyphenols on vascular function. Other studies performed in women have observed that daily doses of 15–20 g of alcohol as red wine are sufficient to elicit protective effects similar to those observed in men who consumed higher doses of wine. In conclusion, moderate consumption of wine exerts a protective effect on biomarkers related to the progression and development of atherosclerosis due to its alcoholic (ethanol) and non-alcoholic (polyphenols) content. Women are more sensitive to the beneficial effects of wine.

Keywords: Wine, alcohol, polyphenols, cardiovascular disease, oxidative stress, inflammation

1. Introduction

The healthy effects of wine are known from ancient times. In fact, wine has been used in old medicine as an antiseptic, a painkiller and as a treatment for several dermatological and digestive disorders [46]. In addition, wine has been closely associated with healthy diets, particularly in Mediterranean countries [49] and many people have attributed great benefits to wine consumption with no scientific basis. The first modern evidence of a scientific link between alcohol consumption and cardiovascular disease was made in the early part of the last century, when it was observed in necropsy studies that individuals that died from alcoholic cirrhosis had cleaner arteries than they ought to according to their age and lifestyle habits, suggesting that alcohol could exert a protective effect against atherosclerosis. Many years later, in the 1970s, several researchers started to scientifically study the relationship between alcohol consumption and overall mortality or other hard end-points such as coronary heart disease [12], stroke [34], peripheral arterial disease [35] and heart failure [16]. The overall conclusion

*Corresponding author: R. Estruch, E-mail: restruch@clinic.ub.es.

ISSN 1879-7717/14/$27.50

of these studies is that people consuming one to two standard drinks per day showed a lower cardiovascular event rate than subjects abstaining from alcohol and those with high alcohol intake [47], a relationship described as J-shaped (or U-shaped) curve [11, 56].

Most of these epidemiological studies correlating moderate alcohol intake with protector effects on the cardiovascular system did not take into account the type of beverage consumed. However, after the description of the French Paradox 20 years ago, part of the research was focused on the protective effects of moderate wine intake compared to the effects of other alcoholic beverages, mainly beer and spirits. Based on epidemiological data, the term "French Paradox" was used to describe the low incidence of cardiovascular disease and the mortality of French population despite their high intake of dietary saturated fats. This paradox has been attributed to moderate wine consumption by the French population, but it was not related to alcohol (ethanol) contained in wine, since plasma high-density lipoprotein cholesterol (HDLc) concentrations were similar to those observed in other countries with a higher prevalence of coronary heart disease that consume mainly other alcoholic beverages [44]. From the beginning, the French Paradox received several criticisms [6, 32], opened an interesting debate as to which type of alcoholic beverage is more cardioprotective than the others and triggered several studies on the effects of the different components of red wine, mainly alcohol and polyphenols on the health, but especially on cardiovascular system. However, the debate continues; the key question related to alcoholic beverages continues to be whether the beneficial effects of moderate consumption of alcoholic beverages is due to ethanol, to their polyphenolic content, or both.

2. Negative effects of alcoholic beverages

It is always important to remember that excessive alcohol intake induces the appearance of several chronic diseases including chronic alcoholism, liver disease, pancreatitis, different types of encephalopathy and neurodegenerative diseases, peripheral neuropathy, myopathy and also cardiomyopathy (Table 1). In fact, chronic alcohol intake gives rise to acute and chronic effects on the cardiovascular system. Among the acute effects, the most frequent action of ethanol on the heart is to induce cardiac arrhythmias. Clinicians have long recognized the temporal association of binge drinking and the onset of atrial fibrillation, especially during weekends, a disease known as the "holiday heart syndrome". In addition, high alcohol intake may provoke ventricular tachyarrhythmias and sudden death. A quarter of the young or middle-aged adult sudden deaths are related to an overdose of alcohol, especially in those who suffer from a subclinical cardiomyopathy [24]. On the other hand, the main chronic effects of maintained high ethanol intake on the cardiovascular system are dilated cardiomyopathy and arterial hypertension. The development of an alcoholic cardiomyopathy requires the consumption of high amounts of ethanol during more than 10 years. In our experience, the first clinical features of alcoholics with dilated cardiomyopathy is usually observed when the subject have drunk a total lifetime dose of ethanol higher than 20 kg of ethanol/kg of body weight [57]. High alcohol intake also produces an increase of blood pressure, whereas alcohol abstinence reduces systolic and diastolic blood pressures to normal or near normal values [18]. In the Framingham study the prevalence of hypertension was double in people who consumed great amounts of alcohol compared with the moderate consumers. However, not all who have consumed high amounts of alcohol develop dilated cardiomyopathy. Great individual vulnerability has been reported in the toxic effects of alcohol. Thus, women and relatives of patients with alcoholic cardiomyopathy have a higher prevalence of cardiac dysfunction compared to men or non relatives who have consumed the same amounts of alcohol [58]. This individual vulnerability to the organic injuries by alcohol has been attributed to some genetic characteristics of the subjects. As an example, a close relationship has been observed between alcoholic cardiomyopathy and polymorphism of the gene of the angiotensin-converting enzyme [21].

3. Positive effects of moderate wine consumption on cardiovascular system

On the other hand, several studies have shown that moderate alcohol consumption mainly in the form of wine could have beneficial effects (protective) on health (Table 1). Up to now, the cardioprotective effect of moderate consumption of wine or alcohol has been documented in several ecological, epidemiological, necropsy, case-control and cohort studies performed

Table 1
Positive (moderate intake) and negative effects (excessive intake) of alcoholic beverages

Effects of the consumption of alcoholic drinks	
Negative	Positive
• Alcoholic dependence	Reduction of:
• Liver cirrhosis	• Global mortality
• Acute and chronic pancreatitis	• Cardiovascular disease
• Dilated cardiomyopathy	• Cancer
• Encephalopathies	• Alzheimer disease
• Polyneuritis	• Diabetes mellitus
• Myopathy	• Renal and vesicular lithiasis
• Fetal alcoholic syndrome	• Rheumatoid arthritis,
• Accidents and violence	...

in countries such as France, Denmark, Yugoslavia, the United States, China and New Zealand [59]. In ecological studies, all but one study reported a significant inverse correlation between wine consumption and mortality due to coronary heart disease [53]. Prospective cohort studies are the most reliable type of study in this respect, because there is a link between exposure and outcome at the individual level and the problem of confounding may be overcome by adjustment techniques. In a great number of epidemiologic studies, the effects of the three main types of alcoholic drinks (wine, beer and distilled drinks) on the cardiovascular system have been analysed. In the latest meta-analysis of Constanzo et al. [12], the authors analysed the effects of the consumption of wine on cardiovascular risk separately from beer and spirits and after the joint analysis of 16 studies they confirmed a J-shape relationship between wine intake and vascular risk, with a maximal protection of 31% (95% confidence interval (CI): 19–43%) at 21 g/d of alcohol. Interestingly, the results of the studies differed depending on the continent where were performed. Thus, in many epidemiological studies from United States, especially those based on the registries of the Nurse's Health Study [17] or the Health Professionals Follow-up Study [33] no differences were found between the protective effects of the moderate consumption of the different types of drink consumed, whereas in some European studies such as the Copenhagen City Heart Study [22] or the one carried out in the east of France [44] found a high significant relation between low or moderate consumption of wine and a lower mortality by cardiovascular disease. Results of more recent cohort studies have confirmed that, among patients with established heart disease or at high-risk of developing this disease, moderate consumption of wine is associated with a lower incidence of cardiovascular events and total mortality as compared with no drinkers [24, 31, 37, 48]. Part of these discrepancies may be due to different confounding factors difficult to strictly control in even prospective cohort studies. Thus, the pattern of drinking is absolutely different in Mediterranean countries form Anglo-Saxon countries [48] and, more important, wine drinkers usually consume healthy foods compared to beer and liquor drinkers [25].

The best way to solve these discrepancies is to perform randomized clinical trials that allow an optimal control of these confounding factors. In addition, the scientific evidence of these trials is higher than that of the cohort trials. However, interventional clinical trials regarding alcoholic beverages must contemplate several ethical considerations and the length of these studies is limited because of the personal difficulties to accomplish interventions, thus, well-designed randomized clinical trials which evaluate hard end-points as final variables are warranted. In the meanwhile, randomized clinical trials that evaluate intermediate markers of cardiovascular risk allow us to assess the differences in effects of the different alcoholic beverages on the cardiovascular system, always within the context of moderate intake.

4. Insulin sensitivity and type 2 diabetes mellitus

Diabetes mellitus is one the main risk factors of cardiovascular disease. Two meta-analyses of 15 and 20 cohort studies [3, 40] pointed out that moderate drinkers show a lower incidence of type 2 diabetes mellitus than lifetime abstainers or excessive consumers, with an apparent J-shape association. This effect seemed to be independent of the type of alcoholic beverage consumed. However, in other prospective studies, the inverse association between moderate alcohol consumption and lower diabetes risk was most apparent in women who reported to drink preferentially wine or beer than in those who consumed liquor [60]. This beneficial effect has been related to improved insulin sensitivity enhancing insulin secretion, pancreatic β-cell survival and/or glucose uptake by peripheral tissues, among others.

However, the results of clinical studies examining the effects of moderate alcohol intake and the different

types of alcoholic beverages have been inconsistent. Some studies have reported no significant changes in insulin sensitivity after intake of wine or spirits [4, 36, 51], whereas others have reported an improvement with any beverage [14, 27]. In this respect, a recent randomized trial performed in high-risk men, moderate dealcoholized red wine and red wine, but not gin significantly improved insulin sensitivity [9], suggesting that polyphenols may play a key role in the prevention of diabetes. In fact, intervention studies with grapes and grape seed extract improved glycemic status in type 2 diabetic patients [38, 62]. Thus, moderate alcohol intake, mainly in the form of wine, helps to maintain or even improve insulin sensitivity. However, more studies are warranted on this issue.

5. Lipid effects

Increase of plasma HDL-cholesterol is the most well-described effect of moderate alcohol consumption, and until recently, this was considered as the main protector effect of alcohol intake on cardiovascular system. This effect is observed after the consumption of any alcoholic beverage in a dose-dependent manner, and, accordingly, it is considered to be due to ethanol itself [5]. Ethanol also seems to increase ApoA-I and II [9, 20]. The effects on triglycerides, LDL-cholesterol and lipoprotein (a) are still under debate. There are several limitations analyzing these effects since the different studies performed have different lengths, some variables analyzed have a longer half-life time than that analyzed, especially in cross-sectional studies, and differences in the characteristics of the participants, such as age, sex, and cardiovascular risk factors, limit the comparison between studies. However, despite of these limitations, a J-shape increase of presenting high triglycerides was observed among 2014 hypertensive men, with the lowest plasma triglyceride concentrations being found in moderate alcohol consumers [41]. LDL-concentrations do not change after moderate alcohol consumption [5]. In respect to lipoprotein (a), a meta-analysis [5] pointed out that moderate alcohol intake has no effect on this variable, but in two clinical trials performed in healthy men [20] and high-risk subjects [9] adjusted mean lipoprotein (a) was significantly reduced after red wine, but not after gin interventions. Thus, given the paucity of effective therapy for elevated lipoprotein (a), the potential lowering efficacy of ethanol and/or polyphenols deserves further research. However, since grapes, grape juice and grape extracts positively modify cholesterol homeostasis [26, 49] and red wine is more effective than white wine changing lipid profile, wine polyphenols also play a role on lipid changes observed in moderate drinkers [23].

6. Effects on blood pressure and endothelial function

Although the negative effects of heavy and binge alcohol drinking on blood pressure are well known, the effects of moderate alcohol consumption are controversial, since some studies have observed a linear trend and others a non-linear or even a J-shaped association [2, 10]. A meta-analysis has pointed out that alcohol consumption increases the risk of hypertension in dose-dependent manner [54] and reduction of alcohol consumption leads to a decrease in blood pressure also in a dose-response relationship [61]. However, moderate alcohol intake, especially in the form of red wine, seems to reduce blood pressure. In fact, *in vitro* and experimental studies have shown a blood pressure lowering effect and an enhancement of endothelial nitric oxide production [15]. However these results are difficult to extrapolate to humans since the amount of polyphenols from red wine used in these studies is usually higher than that achieved in plasma through moderate wine intake. In a recent 4-week intervention cross-over clinical trial, moderate doses of dealcoholized red wine decreased systolic and diastolic blood pressure while increasing plasma NO concentration. Red wine tended to have similar effects to those of dealcoholized red wine, but the changes did not achieve statistical significance, and gin had no effect. Thus, these blood pressure-lowering effects and NO-raising effects should be attributed to red wine polyphenols and not to alcohol [7].

On the other hand, the effects of moderate alcohol intake on endothelial function remain controversial. In a multiethnic cross-over study, those subjects who drank between >1 drink/month and 2 drinks/day showed a higher flow-mediated dilation (FMD) than non drinkers or those who drank more than 2 drinks/day, independent of the type of alcoholic beverage consumed [52]. However, in randomized intervention trials, 30 g of alcohol as red wine showed significant beneficial effects on endothelial function 1–4 h after ingestion, while beer and white wine had a borderline effect and whiskey exerted no effect [55].

In other studies either red wine and dealcoholized red wine decreased plasma endothelin-1 concentration [39]. Thus, it seems that red wine polyphenols exert a beneficial effect on endothelial function but this effect do not persist >4 h.

7. Thrombosis and fibrinolysis system

Heavy alcohol intake has been associated with lower fibrinolytic capacity, a more procoagulant state and a higher blood viscosity, whereas moderate alcohol consumption is consistently associated with a decreased procoagulant state and blood viscosity, as well as a higher fibrinolytic capacity. In a meta-analysis, consumption of less than 12 g of ethanol/day was significantly associated with a decreased relative risk of total stroke [45]. In addition, in population studies, alcohol consumption was associated with a reduced risk of venous thrombosis and lower fibrinogen levels [42]. In randomized clinical trials, plasma fibrinogen levels decreased after red wine and gin intake, suggesting that this effect is due to ethanol contained in alcoholic beverages [20]. Other positive effects of moderate alcohol intake on hemostatic system include inhibition of platelet aggregation and reduction of concentration of tissue factor and factors VII, VIII and VIII-von Willebrand. Wine, by itself, also increases plasminogen activator-1/plasminogen activator (PAI-1/tPA) ratio. Therefore, the anticoagulant effect of moderate alcohol consumption seems to be effective in both healthy subjects and patients with a pro-coagulant profile. However, a linear relationship between increased alcohol consumption and risk of hemorrhagic stroke was also observed.

8. Mechanisms of the cardioprotective effect of moderate wine intake

The beneficial effects of moderate wine intake on the cardiovascular system have been related to their action on oxidative status and inflammation of the arterial wall.

8.1. Oxidative status

While alcohol itself is known to induce oxidative stress, several *in vitro* studies regarding polyphenols from wine, beer, and vegetables have shown that these compounds exert an antioxidant effect. Accordingly, it seems that there are a counteracting effect between polyphenols and alcohol. Several clinical trials have shown that red wine increases plasma antioxidant capacity, suppresses reactive oxygen species generation, reduces plasma malondialdehide, prolongs lag phase time of low-density lipoprotein (LDL) particles and decreases oxidative DNA damage [20]. By contrast, ethanol decreases antioxidant and increases lipoperoxidation serum parameters [1]. In addition, a postprandial reduction of oxidative stress has also been observed after red wine consumption [13], an interesting effect that help to promote the consumption of wine always with meals.

8.2. Inflammation

Atherosclerosis is considered a low-grade inflammatory disease. In a meta-analysis [5], the association between alcohol intake and plasma concentration of different inflammatory biomarkers related to atherosclerosis, such as C-reactive protein (CRP), interleukin 6 (IL-6) and tumour necrosis factor-α (TNF-α) was not significant. However, when the type of alcoholic beverage was considered, the results differed. In a 4-week randomized cross-over trial, red wine and gin decreased IL-1α, but only red wine but not gin diminished plasma CRP in healthy subjects [19], explaining why CRP is not affected when only alcohol is considered. In addition, the effects are not the same in high-risk vascular subjects, since alcohol (red wine and gin) increased the anti-inflammatory IL-10 and decreased IL-16, and red wine but not gin decreased plasma IL-6 concentration [8].

Cell adhesion molecules and cytokines are other inflammatory biomarkers related to atherosclerosis since these molecules participate in the recruitment of circulating leukocytes to the vascular endothelium and further migration to subendothelial spaces, initiating the atherosclerotic process. In healthy volunteers [19] significant reductions of vascular cellular adhesion molecule-1 (VCAM-1), intercellular CAM-1 (ICAM-1), very late antigen-4 (VLA-4) lymphocyte expression and lymphocyte function associated antigen-1 (LFA-1), macrophage-1 antigen (Mac-1), VLA-4 and monocyte chemoprotein-1 (MCP-1) monocyte expression were observed after red wine, but not after gin intake. Again, the effects in high-risk subjects were different but protective [8].

Table 2
Mechanisms of the positive and negative effects of the moderate consumption of alcoholic drinks with (wine) and without (gin) polyphenols [15]

Effects of Alcoholic Drinks without Polyphenols (GIN)	
Positive	Negative
On lipoproteins	*On plasmatic homocysteine*
Increase in HDL-cholesterol	Increase in total homocysteine
Reduction of lipoprotein a	Reduction in folic acid
Reduction of the oxidation of LDL-cholesterol	
On the metabolism of the glucose	
Increase in the sensitivity to the insulin	
On the inflammation markers	
Reduction of C-reactive protein	
Reduction of ICAM-1 and VCAM-1	
Reduction of interleukin-1	
Reduction of fibrinogen	
On haemostasis	
Reduction of platelet aggregation	
Reduction of the tissue factor	
Reduction of factor VII, VIII and VIII-von Willebrand	
Effects of Alcoholic Beverages with Polyphenols (WINE)	
Positive	Negative
On lipoproteins	None
Increase in HDL-cholesterol	
Reduction of lipoprotein a	
Reduction of the oxidation of LDL-cholesterol	
On the metabolism of the glucose	
Increase in sensitivity to insulin	
On the inflammation markers	
Reduction of reactive protein C	
Reduction of ICAM-1 and VCAM-1	
Reduction of interleukin-1	
Reduction of molecules of adhesion LFA-1, Mac-1, VLA-4 and chemokine MCP-1 in circulating monoliths	
Inhibition of nuclear factor κB	
Reduction of fibrinogen	
On the hemostasis	
Reduction of platelet aggregation	
Reduction of the tissue factor	
Reduction of factor VII, VIII and VIII-vW	
Increase in the tissue factor of plasminogen	
Increase in the activity of PAI-1	
On the vascular function	
Increase in the coronary vasodilatation induced by adenosine.	

9. Summary

Although heavy or binge alcohol consumption leads to an increase in the risk of all-causes death and makes up a enormous social and economical problem that must be addressed, moderate alcohol consumption, especially in the form of wine, has cardioprotective effects through different mechanisms. Moderate wine consumption improves glucose metabolism, lipid profile, endothelial function and coagulation and platelet function throughout their anti-oxidant and anti-inflammatory effects (Table 2). All these protective effects explain the reduction in overall and cardiovascular mortality of moderate wine drinkers reported in some epidemiological studies. Nevertheless, although they are hard to carry out and need careful ethical considerations, more long-term clinical trials are needed to elucidate whether other mechanisms may be involved

in these protective effects and which type of alcoholic beverage is more cardioprotective with the highest level of scientific evidence.

Acknowledgements

CIBERobn is an initiative of ISCIII, Spain. This work was supported by grants from the *Ministerio de Ciencia e Innovación* (AGL2009-13906-C02-02 and AGL2010-22319-C03-02 INNPRONTA Program, INCOMES IPT-2011108).

References

[1] Addolorato G, Leggio L, Ojetti V, Capristo E, Gasbarrini G, Gasbarrini A. Effects of short-term moderate alcohol administration on oxidative stress and nutritional status in healthy males. Appetite. 2008;M50:50-6.

[2] Andersen UO, Jensen GB. Population blood pressure and low moderate alcohol intake in untreated population followed over 20 years. Copenhagen City Heart Study. Eur Heart J. 2011;32:3081-7.

[3] Baliunas DO, Taylor BJ, Irving H, Roerecke M, Patra J, Mohapatra S, Rehm J. Alcohol as a risk factor for type 2 diabetes: A systematic review and meta-analysis. Diabetes Care. 2009;32:2123-32.

[4] Beulens JW, van Beers RM, Stolk RP, Schaafsma G, Hendriks HFJ. The effect of moderate alcohol consumption on fat distribution and adipocytokines. Obesity (Silver Spring). 2006;14:60-6.

[5] Brien SE, Ronksley PE, Turner BJ, Mukamal KJ, Ghali WA. Effect of alcohol consumption on biological markers associated with risk of coronary heart disease: Systematic review and meta-analysis of interventional studies. BMJ. 2011;342:d636.

[6] Chawla, R. Regular drinking might explain the French paradox. Br Med J. 2004;329:1308.

[7] Chiva-Blanch G, Urpi-Sardá M, Ros E, Arranz S, Valderas-Martínez P, Casas R, Sacanella E, Llorach R, Lamuela-Raventós RM, Andrés-Lacueva C, Estruch R. Dealcoholized red wine decreases systolic and diastolic blood pressure and increases plasma nitric oxide: Short communication. Circ Res. 2012a;111:1065-8.

[8] Chiva-Blanch G, Urpi-Sarda M, Llorach R, Rotches-Ribalta M, Guillén M, Casas R, Arranz S, Valderas-Martinez P, Portoles O, Corella D, Tinahones F, Lamuela-Raventos RM, Andres-Lacueva C, Estruch R. Differential effects of polyphenols and alcohol of red wine on the expression of adhesion molecules and inflammatory cytokines related to atherosclerosis: A randomized clinical trial. Am J Clin Nut. 2012b;95:326-34.

[9] Chiva-Blanch G, Urpi-Sarda M, Ros E, Valderas-Martínez P, Casas R, Arranza S, Guillén M, Lamuela-Raventós RM, Llorach R, Andrés-Lacueva C, Estruch R. Effects of red wine polyphenols and alcohol on glucose metabolism and the lipid profile: A randomized clinical trial. Clin Ntr. 2013a;32: 200-6.

[10] Chiva-Blanch G, Arranz S, Lamuela-Raventós RM, Estruch R. Effects of wine, alcohol and polyphenols on cardiovascular disease risk factors: Evidences from human studies. Alcohol Alcohol. 2013;48:270-7.

[11] Connor J. The life and times of the J-shape curve. Alcohol Alcohol. 2006;41:583-4.

[12] 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.

[13] Covas MI, Gambert P, Fito M, de la Torre R. Wine and oxidative stress: up-to-date evidence of the effects of moderate alcohol consumption on oxidative damage in humans. Atherosclerosis. 2010;208:297-304.

[14] Davies MJ, Baer DJ, Judd JT, Brown ED, Campbell WS, Taylor PR. Effects of moderate alcohol intake on fasting insulin and glucose concentrations and insulin sensitivity in postmenopausal women: A randomized controlled trial. JAMA. 2002;287:2559-62.

[15] Diebolt M, Bucher B, Andriantsitohaina R. Wine polyphenols decrease blood pressure, improve NO vasodilatation, and induce gene expression. Hypertension. 2001;38:159-65.

[16] Djousse L, Gaziano JM. Alcohol consumption and heart failure: A systematic review. Curr Atheroscler Rep. 2008;10:117-20.

[17] Djousse L, Lee IM, Buring JE, Graziano JM. Alcohol consumption and risk of cardiovascular disease and death in women – Potential mediating mechanisms. Circulation. 2009;120:237-44.

[18] Estruch R, Sacanella E, De la Sierra A, Aguilera MT, Antunez E, Nicolas JM, Fernández-Solá J, Coca A, Urbano-Márquez A. Effects of alcohol withdrawal on 24 hour ambulatory blood pressure among alcohol-dependent patients. Alcohol Clin Exp Res. 2003;27:2002-8.

[19] Estruch R, Sacanella E, Badia E, Antúnez E, Nicolás JM, Fernández-Solá J, Rotilio D, de Gaetano G, Rubin E, Urbano-Márquez A. 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.

[20] Estruch R, Sacanella E, Mota F, Chiva-Blanch G, Antúnez E, Casals E, Deulofeu R, Rotilio D, Andres-Lacueva C, Lamuela-Raventos RM, de Gaetano G, Urbano-Marquez A. Moderate consumption of red wine, but not gin, decreases erythrocyte superoxide dismutase activity: A randomised cross-over trial. Nutr, Metab Cardiovasc Dis. 2011;21:46-53.

[21] Fernández-Solà J, Nicolás JM, Oriola J, Sacanella E, Estruch R, Rubin E, Urbano-Márquez, A. Angiotensin-converting enzyme gene polymorphism is associated with vulnerability to alcoholic cardiomyopathy. Ann Intern Med. 2002;145: 1-11.

[22] Gronbaek M, Becker U, Johansen D, Gottschau A, Schnohr P, Ole Hein H, et al. Type of alcohol consumed and mortality from all causes, coronary heart disease, and cancer. Ann Intern Med. 2000;133:411-9.

[23] Guilford JM, Pezzuto JM. Wine and health: A review. Am J Enol Vitic. 2011;62:471-86.

[24] Hansel B, Thomas F, Pannier B, Bean K, Kontush A, Chapman MJ, et al. Relationship between alcohol intake, health and social status and cardiovascular risk factors in the urban

Paris-Ile-De-France Cohort: Is the cardioprotective action of alcohol a myth? Eur J Clin Nutr. 2010;64:561-8.
[25] Hansel B, Roussel R, Diguet V, Deplaude A, Chapman MJ, Bruckert E. Relationship between consumption of alcoholic beverages and healthy foods: The French supermarket cohort of 196.000 subjects. Eur J Prev Cardiol. (in press).
[26] Jimenez JP, Serrano J, Tabernero M, Arranz S, Díaz-Rubio ME, García-Diz L, et al. Effects of grape antioxidant dietary fiber in cardiovascular risk factors. Nutrition. 2008;24:646-53.
[27] Kim SH, Abbasi F, Lamendola C, Reaven GM. Effect of moderate alcoholic beverage consumption on insulin sensitivity in insulin-resistant, nondiabetic individuals. Metabolism. 2009;58:387-392.
[28] 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.
[29] Kupari M, Koskinen P. Alcohol, cardiac arrthymias and sudden death. Novartis Found Symp. 1998;216:68-79.
[30] Lemmens PHHM, Individual risk and population distribution of alcohol consumption. Holder HD, Edwards G. (eds) Alcohol and public policy: Evidence and issues. Oxford: Oxford University Press, 1995;38-61.
[31] Levantesi G, Marfisi R, Mozaffarian D, Franzosi MG, Maggioni A, Nicolisi GL, et al. Wien consumption and risk of cardiovascular events after myocardial infarction: Results from the Gizzi-Prevenzione Trial. Int J Cardiol. 2013;163:282-7.
[32] Lindberg MI, Amsterdam EA. Alcohol, wine and cardiovascular health. Clin Cardiol. 2008;31:347-51.
[33] Mukamal KJ, Conigrave KM, Mittlemen MA, Camargo CA, Jr., Stampfer MJ, Willett WC, et al. Roles of drinking pattern and type of alcohol consumed in coronary heart disease in men. N Engl J Med. 2003;348:109-18.
[34] Mukamal KJ, Ascherio A, Mittleman MA, Conigrave KM, Camargo CA, Jr., Kawachi I, et al. Alcohol and risk for ischemic stroke in men: The role of drinking patterns and usual beverage. Ann Intern Med. 2005;142:11-9.
[35] Mukamal KJ. Alcohol intake and noncoronary cardiovascular diseases. Ann Epidemiol. 2007;17:S8-S12.
[36] Naissides M, Mamo JCL, James AP, Pal S. The effect of chronic consumption of red wine on cardiovascular disease risk factors in postmenopausal women. Atherosclerosis. 2006;185: 438-45.
[37] Perissinotto E, Buja A, Maggi S, Enzi G, Manzato E, Scafato E, et al. Alcohol consumption and cardiovascular risk factors in older lifelong wine drinkers: The Italian Longitudinal Study on Aging. Nutr Metab Cardiovasc Dis. 2010;20:647-55.
[38] Kar P, Laight D, Rooprai HK, Skaw KM, Cummings M. Effects of grape seed extract in Type 2 diabetic subjects at high cardiovascular risk: A double blinf randomized placebo controlled trial examining metabolic markers, vascular tone, inflammation, oxidative stress and insulin sensititivity. Diabet Med. 2009;26:526-31.
[39] Kiviniemi TO, Saraste A, Lehtimäki T, Toikka JO, Saraste M, Raitakari OT, Hartiala JJ, Viikari J, Koskenvuo JW. Decreased endothelin-1 levels after acute consumption of red wine and de-alcoholized red wine. Atherosclerosis. 2010;211:283-6.
[40] 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.
[41] Park H, Kim K. Association of alcohol consumption and lipid profile in hypertensive men. Alcohol Alcohol. 2012;47:282-7.
[42] Pomp ER, Rosendaal FR, Doggen CJ. Alcohol consumption is associated with a decreased risk of venous thrombosis. Thromb Haemost. 2008;99:59-63.
[43] Renaud S, de Lorgeril M. Wine, alcohol, platelets and the French paradox for coronary heart disease. Lancet. 1992;339:1523-6.
[44] Renaud S, Guéguen R, Siest G, Salamon R. Wine, beer, and mortality in middle-aged men from eastern France. Arch Intern Med. 1999;159:1865-70.
[45] Reynolds K, Lewis B, Nolen JD, Kinney GL, Sathya B, He J. Alcohol consumption and risk of stroke: A meta-analysis. JAMA. 2003;289:579-88.
[46] Robinson J. The Oxford Companion to Wine. New York: Oxford University Press, 2006.
[47] Ronksley PE, Brien SE, Turner BJ, Mukamal KJ, Ghali WA. Association of alcohol consumption with selected cardiovascular disease outcomes: A systematic review and meta-analysis. Br Med J. 2011;342:d671.
[48] Ruidavets JB, Ducimetiere P, Evans A, Montaye M, Haas B, Bingham A, et al. Patterns of alcohol consumption of ischaemic heart diseased in cultured divergent countries: The Prospective Epidemiological Study of Myocardial Infarction (PRIME). BMJ. 2010;341:C6077.
[49] Sano A, Uchida R, Saito M, Shioya N, Komori Y, Tho Y, et al. Beneficial effects of grape see extract on malondialdehyde-modifief LDL. J Nutr Sci Vitaminol. 2007;53:174-82.
[50] Serra-Majem L, Roman, D, Estruch, R. Scientific evidence of interventions using the Mediterranean diet: A systematic review. Nutr Rev. 2006;64:S27-47.
[51] Sierksma A, Patel H, Ouchi N, Kihara S, Funahashi F, Heine RJ, et al. Effect of moderate alcohol consumption on adiponectin, tumor necrosis factor-alpha, and insulin sensitivity. Diabetes Care. 2004;27:184-9.
[52] Suzuki K, Elkind MS, Boden-Albala B, Jin Z, Berry G, Di Tullio MR, Sacco RL, Homma S. Moderate alcohol consumption is associated with better endothelial function: A cross sectional study. BMC Cardiovasc Disord. 2009;9:8.
[53] Svärdsudd, K. Moderate alcohol consumption and cardiovascular disease: Is there evidence for a preventive effect? Alcohol Clin Exp Res. 1998;22:307S-14S.
[54] Taylor B, Irving HM, Baliunas D, Roerecke M, Patra J, Mohapatra S, Rehm J. Alcohol and hypertension: Gender differences in dose-response relationships determined through systematic review and meta-analysis. Addiction. 2009;104:1981-90.
[55] Tousoulis D, Ntarladimas I, Antoniades C, Vasiliadou C, Tentolouris C, Papageorgiou N, Latsios G, Stefanadis C. Acute effects of different alcoholic beverages on vascular endothelium, inflammatory markers and thrombosis fibrinolysis system. Clin Nutr. 2008;27:594-600.
[56] Thompson PL. J-curve revisited: Cardiovascular benefits of moderate alcohol use cannot be dismissed. MJA. 2013;198:419-22.
[57] Urbano-Márquez A, Estruch R, Navarro-López F, Grau JM, Mont L, Rubin E. Effects of alcoholism on the skeletal and cardiac muscle. N Engl J Med. 1989;301:28-33.

[58] Urbano-Márquez A, Estruch R, Fernández-Solá J, Nicolás JM, Paré JC, Rubin E. The greater risk of alcoholic cardiomyopathy and myopathy in women compared with men. JAMA. 1995;274:149-54.
[59] Veenstra, J. Moderate alcohol use and coronary heart disease: An U-shaped curve? Simopoulos AP, (ed) Impact on nutrition and health, Basel: World Rev Nutr Diet. Karger, 1991;38-71.
[60] Wannamethee SG, Camargo CA, Jr., Manson JE, Willett WC, Rimm EB. Alcohol drinking patterns and risk of type 2 diabetes mellitus among younger women. Arch Intern Med. 2003;163: 1329-36.
[61] Xin X, He J, Frontini MG, Ogden LG, Motsamai OI, Whelton PK. Effects of alcohol reduction on blood pressure: A meta-analysis of randomized controlled trials. Hypertension. 2001;38:1112-7.
[62] Zunino S. Type 2 diabetes and glycemic response to grapes or grape products. J Nutr. 2009;139:1794S-1800S.