*Alcohol & Alcoholism* Vol. 37, No. 5, pp. 409–415, 2002

**REVIEW**

# CARDIOPROTECTIVE EFFECTS OF LIGHT–MODERATE CONSUMPTION OF ALCOHOL: A REVIEW OF PUTATIVE MECHANISMS

DHARAM P. AGARWAL

Institute of Human Genetics, University of Hamburg, 22529 Hamburg, Butenfeld 42, Germany

(*Received* 19 *October* 2001; *in revised form* 14 *March* 2002; *accepted* 8 *April* 2002)

**Abstract** — There is abundant epidemiological and clinical evidence showing that light–moderate drinking is associated with a reduced risk of coronary heart disease (CHD), total and ischaemic stroke and total mortality in middle-aged and elderly men and women. The epidemiological evidence suggests a J- or U-shaped relationship between alcohol and CHD. However, the apparent benefits of moderate drinking on CHD mortality are offset at higher drinking levels by increasing risk of death from other types of heart diseases (cardiomyopathy, arrhythmia etc.), neurological disorders, cancer, liver cirrhosis, and traffic accidents. The plausible mechanisms for the putative cardioprotective effects include increased levels of high-density lipoprotein cholesterol, decreased levels of low-density lipoprotein cholesterol, prevention of clot formation, reduction in platelet aggregation, and lowering of plasma apolipoprotein(a) concentration. Thus, alcohol reduces the risk of coronary vascular diseases both by inhibiting the formation of atheroma and decreasing the rate of blood coagulation.

## INTRODUCTION

Drinking excessive amounts of alcohol regularly for years is toxic to almost every tissue of the body. Many of the toxic effects of alcohol are due to disturbances of a wide variety of metabolic functions and organ damage. Long-term alcohol use increases the risk of liver disease, heart disease, peptic ulcers, certain types of cancers, complicated pregnancies, birth defects, and brain damage (Agarwal and Seitz, 2001). Heavy or binge drinking may even result in respiratory depression and death. Alcohol use can also cause mood changes and loss of inhibitions as well as violent or self-destructive behaviour.

On the other hand, epidemiological and clinical evidence shows that light–moderate drinking is associated with a reduced risk of coronary heart disease (CHD), total and ischaemic stroke and total mortality in middle-aged and elderly men and women (Doll, 1997; Grobbee *et al*., 1999; Rimm *et al*., 1999; Klatsky, 2001; Rotondo *et al*., 2001; van Tol and Hendriks, 2001). The evidence suggests a J- or U-shaped relationship between alcohol and CHD. This article reviews the epidemiological evidence for alcohol's putative cardioprotective effects and discusses the plausible underlying biological mechanisms.

## CONCEPT OF LIGHT–MODERATE DRINKING

Alcohol intake is frequently expressed in 'drinks' or 'units' that vary with beverage type, culture and era. Alcohol drinking may be divided into 'light', 'moderate' and 'heavy' categories, depending upon the amount of alcohol consumed in terms of pure ethanol per day (Dufour, 1999; Kalant and Poikolainen, 1999). 'Light–moderate' alcohol intake is usually defined as an average consumption of 1 to 2 drinks per day; 'heavy drinking' indicates usual intake of ≥3 drinks per day of wine, liquor, or beer. In absolute terms, amounts of alcohol consumed <30 g/day are taken as light–moderate drinking, amounts of pure alcohol consumed >30 g per day are considered as heavy drinking. Whereby drinking pattern, type of beverage, gender, and age are important parameters in defining moderate and heavy drinking.

## ALCOHOL AND CHD MORBIDITY AND MORTALITY

Risk of death from all causes has been found to be significantly lower among men who drink moderately, compared to abstainers. Several epidemiological investigations have shown that a low to moderate level of alcohol intake has a definitive protective role against CHD and stroke. Such conclusions have been based upon epidemiological studies on the risks for heart disease, coronary artery disease and death in individuals with low or moderate alcohol intake, when compared with the corresponding risks in persons who do not consume alcohol at all (Rimm *et al*., 1999; Corrao *et al*., 2000; Meister *et al*., 2000; Agarwal and Srivastava, 2001). The dose–response curve usually is found to be J- or U-shaped, i.e. the risk is higher when alcohol consumption is high, lower when alcohol consumption is low or moderate, and tends to go up again in individuals not consuming any alcohol (Andreasson, 1998; San Jose *et al*., 1999). Level of alcohol consumption that has been associated with lower risk for CHD ranges as widely as from 1 drink daily to ~3 drinks per day (Rimm *et al*., 1999; Gronbaek *et al*., 1999). When all cohort data of the above-mentioned studies are combined, there appears to be a decline in the risk for myocardial infarction at doses up to 1 drink per day, with little further change in risk associated with increased alcohol intake (Rimm *et al*., 1999). Berger *et al*. (1999) found that light–moderate alcohol consumption reduced the overall risk of stroke and risk of ischaemic stroke in men. The benefit was apparent with as little as 1 drink per week. Greater consumption up to 1 drink per day did not increase the observed benefit. In a Finnish study, Makela *et al*. (1997) observed that, among men aged 30–69 years, the beneficial effects of light–moderate alcohol consumption 'prevented' some 400 CHD deaths each year, which corresponds to 12–14% of the observed CHD deaths. Rimm *et al*. (1999) in their meta-analysis

concluded that alcohol intake (30 g of alcohol per day) is causally related to 24.7% reduction in risk of CHD through changes in lipids, lipoproteins and fibrinogen.

In a more recent meta-analysis relating to alcohol consumption with the risk of CHD (Corrao *et al*., 2000), the risk decreased from drinking levels of 0 to 20 g/day (RR = 0.80; 95% CI); there was evidence of a protective effect up to 72 g/day (RR = 0.96; 95% CI) and increased risk at ≥89 g/day (RR = 1.05; 95% CI). Lower protective effects and harmful effects were found in women, in men living in countries outside the Mediterranean area and in studies where fatal events were used as the outcome.

## ALCOHOL DRINKING PATTERN AND THE RISK OF CHD

The strongest inverse correlation between moderate drinking and CHD has been shown among both men and women who consumed 1–2 drinks per day on 5–6 days per week (McElduff and Dobson, 1997). Rimm *et al*. (1999) observed that men who reported drinking, on average, on 3–4 days per week had a relative risk of 0.66, compared with men who drank less than 1 day a week. Alcohol drinking pattern may also have a profound influence on the blood pressure effects of alcohol. Intervention studies in men have shown acute increases in blood pressure in men who drink predominantly at weekends, compared to longer-term pressor effects in regular daily drinkers (Marques-Vidal *et al*., 2001). The binge-drinking pattern observed among Northern Irish drinkers leads to physiologically disadvantageous consequences regarding blood pressure levels, whereas no such fluctuations in blood pressure levels were found for regular consumption noted among French drinkers (Puddey *et al*., 1999). Hence, exploration of any protective association of alcohol against CHD needs to consider carefully the implications of pattern of drinking for the relationship.

## ALCOHOL AND THE FRENCH PARADOX

The low CHD mortality rate observed in Mediterranean populations in association with red wine consumption and a high saturated fat intake has given rise to what is now popularly termed the ‘French paradox’. This phenomenon refers to people residing in certain parts of France and other Mediterranean countries where red wine is customarily consumed during meals. These populations show a low CHD mortality, despite living a lifestyle considered to have comparably high CHD risks, like those in the USA and many other developed countries (Criqi, 2001). This relationship has been observed in both men and women and in different age groups. Many investigators have claimed that wine is the significant factor explaining the French paradox (see below).

## PUTATIVE BIOLOGICAL MECHANISMS UNDERLYING THE CARDIOPROTECTION

Most of the prospective cohort studies have consistently shown that moderate alcohol intake has a protective effect against CHD (Leighton *et al*., 1997; McKee and Britton, 1998; Rimm *et al*., 1999; Gaziano *et al*., 2000). As shown in Table 1, several factors have been proposed to explain the beneficial effects of moderate alcohol consumption on the development of CHD and atherosclerosis (Srivastava *et al*., 1994; Grobbee *et al*., 1999; Goldberg and Soleas, 2001; Rotondo *et al*., 2001). These include effects of alcohol on high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), plasma apolipoprotein(a) [Lp(a)] levels, platelet aggregability, blood fibrinolytic activity, insulin sensitivity, oestrogen levels, and stress. The following is a discussion of these factors.

### *Increase in HDL*

HDL-cholesterol is inversely related to CHD and hence it has been proclaimed that alcohol’s effect is mediated through increased HDL (De Oliviera *et al*., 2000; Sillanaukee *et al*., 2000; Hannuksela and Savolainen, 2001). Cholesteryl ester transfer protein (CETP) mediates the transfer of cholesteryl esters from HDL into very-low-density lipoproteins (VLDL) and LDL with a reciprocal exchange of triglycerides (Krause and Auerbach, 2001). A low transfer rate may reduce the reverse transport of cholesterol (Castilho *et al*., 2001). The plaque regression has been demonstrated angiographically in those persons who received drugs that lower cholesterol and increase HDL, indicating that the reverse cholesterol transport can be

Table 1. Putative biological mechanisms underlying cardioprotection by low–moderate alcohol consumption

| Parameter | Cardioprotective effect of moderate alcohol intake |
|---|---|
| Lipid and lipoprotein profile | Increases protective (‘good’) HDL-cholesterol |
| | Inhibits oxidation of harmful (‘bad’) LDL-cholesterol |
| Thrombosis | Reduces platelet aggregation |
| | Reduces fibrinogen levels |
| | Increases fibrinolysis (the process by which clots dissolve) |
| Cardiovascular system | Increases coronary blood flow |
| | Reduces blood pressure (<1–2 drinks per day) |
| Hormones | Reduces blood insulin levels |
| | Increases blood insulin sensitivity |
| | Increases oestrogen levels |
| Lifestyle | Reduces stress |
| Other effects | Increases paraoxonase activity |
| | Decreases plasma homocysteine levels |

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

enhanced by raising the HDL levels and thereby overcoming the inhibitory effects of oxidized LDL upon the atherogenic process. While it was earlier thought that alcohol increased only HDL-3 and not HDL-2, recent observations have shown that both classes contribute equally and cooperatively to the overall efficiency of reverse transport of cholesterol (Hannuksela and Savolainen, 2001). Hence, alcohol intake may raise plasma HDL levels either by altering the synthesis or clearance of HDL or by effects on enzymes and proteins influencing HDL metabolism. According to Rimm *et al*. (1999), a 16.8% reduction in CHD is directly attributable to increased HDL from consuming 30 g alcohol per day.

*Decreased LDL oxidation*

Many observational studies have provided strong evidence that oxidation of LDL plays an important role in the progression of atherosclerotic vascular disease (Griffin, 1999). In fact, the antioxidative effect of alcohol, in all probability, is exerted by affecting the oxidation of LDL thereby hampering atherosclerotic plaque formation (Serafini *et al*., 2000). Wine contains compounds with antioxidant capacity that could account for its postulated stabilizing effect on LDL. Grape-derived beverages supply a large number of nutritional antioxidants, because of their high content of polyphenols. This might be one of the mechanisms behind the supposed beneficial effect of red wine. Indeed, polyphenolic antioxidants present in red wine have been shown to inhibit the oxidation of human LDL (Puddey *et al*., 1998; van Golde *et al*., 1999). It has recently been shown that distilled alcohol on wood ageing acquires significant amounts of antioxidants which could be different from those present in red wine (Puddey and Croft, 1999). These findings suggest that there might not be large differences between the capabilities of wine (red wine especially) and distilled alcohol in the protection and/or lower risk of heart disease (Goldberg *et al*., 1999).

*Alcohol-related changes in apolipoprotein profile*

Apolipoprotein AI is distributed within high-density lipoprotein (HDL) between different types of particles. Alcohol drinking increases the plasma concentrations of apolipoprotein AI and apolipoprotein AII, the main components of HDL particles (De Oliviera *et al*., 2000). Based upon epidemiological data, it has been estimated that an average individual consuming 30 g of alcohol per day would show an 8 mg/dl increase in the plasma concentration of apolipoprotein AI, primarily due to increased synthesis in liver (Rimm *et al*., 1999).

*Reduction in apolipoprotein(a)*

Recent observational studies showed that Lp(a) plays a significant role in atherosclerosis and is one of the major risk factors for cardiovascular disease (Paassilta *et al*., 1998; Fontana *et al*., 1999). Epidemiologically, Lp(a) is a strong positive risk factor for CHD, the presumed mechanism being the inhibition of fibrinolysis by reduced plasminogen levels due to elevated Lp(a) levels (Testa and Marcovina, 1999). A number of intervention studies in human subjects support the notion that alcohol consumption reduces plasma Lp(a) concentrations. As reported by Kervinen *et al*. (1993), cessation or reduction in beverage alcohol consumption was accompanied by a significant increase in plasma Lp(a). We have earlier demonstrated that CHD patients have higher levels of Lp(a) and those who were alcohol drinkers showed significantly lower Lp(a) levels (Vasisht *et al*., 1996). Further, Paassilta *et al*. (1998) have shown that social drinking is associated with low Lp(a) lipoprotein concentration in middle-aged men and concluded that low Lp(a) lipoprotein concentration may be one factor explaining low mortality and retarded progression of coronary artery disease in social drinkers.

*Reduction in blood clotting and platelet aggregation*

Increased HDL-cholesterol levels can explain only a part of the protective effect of alcoholic beverages (Rimm *et al*., 1999). The other part may be related to decreased platelet activity and other clotting factors. Moderate alcohol consumption may affect several haemostatic factors, including fibrinogen concentration, platelet aggregability and the fibrinolytic factors: tissue-type plasminogen activator and plasminogen activator inhibitor (Djousse *et al*., 2000; Mukamal *et al*., 2001; van de Wiel *et al*., 2001). Plasma fibrinogen concentrations are decreased by moderate alcohol consumption (Hendriks and van der Gaag, 1998; Mennen *et al*., 1999; Lacoste *et al*., 2001). Hence, alcohol has been shown to reduce blood platelet aggregability (Ruf, 1999). According to Rimm *et al*. (1999), the projected percentage reduction in the risk of CHD attributed to effects of alcohol on concentrations of fibrinogen were 4.3 (unadjusted) and 12.5 (adjusted for intraindividual variability), respectively.

The antiplatelet activity of wine is explained not only by ethanol, but also by the polyphenolic components with which red wines are richly endowed. It appears that wine and wine phenolics in particular could significantly inhibit platelet aggregation and that this could explain, at least in part, the protective effect of red wine against atherosclerosis and CHD.

*Light–moderate alcohol consumption reduces blood pressure*

Epidemiological data clearly show higher mean blood pressure and/or hypertension with increasing alcohol drinking (Grobbee *et al*., 1999). Blood pressure effects of alcohol vary according to chronicity and amount of intake. On the other hand, short-term lowering of blood pressure by alcohol is known. A J-shaped relation between alcohol and blood pressure has been suggested with moderate drinkers having a lower blood pressure level, with the lowest levels in consumers of 1 to 3 drinks per day (Gillman *et al*., 1995; Beilin *et al*., 1996).

*Alcohol reduces insulin resistance and increases insulin sensitivity*

Regular moderate alcohol consumption is associated with decreased insulin resistance and this may partly explain the cardioprotective effect of alcohol (Bell *et al*., 2000; Flanagan *et al*., 2000). Moreover, light–moderate alcohol consumption promotes insulin sensitivity of skeletal muscle (Facchini *et al*., 1994). Conceivably, this benefits the protective effects of moderate drinking on vascular health and risk for obesity and diabetes. The mechanism responsible for alcohol's insulin-sensitizing activity remains obscure. McCarty (2001) has proposed that metabolism of acetate in peripheral tissues generates sufficient levels of AMP to temporarily stimulate the AMP-activated protein kinase, which in turn induces the synthesis of certain long-lived proteins that act to boost insulin sensitivity and possibly aid the efficiency of fat oxidation as

well. Moreover, improvement of insulin sensitivity results in higher HDL-cholesterol levels; it is suggested that this is one of the routes taken by alcohol to act upon HDL metabolism (Kiechl *et al*., 1996). Whether interrelated or not, both the HDL-cholesterol increase and enhanced insulin sensitivity are considered to have a beneficial effect on the process of atherosclerosis (Lazarus *et al*., 1997).

*Reduction in plasma homocysteine*

Recent studies suggest that high plasma homocysteine concentrations are an independent risk factor for coronary, cerebral and peripheral arterial occlusive diseases (Danesh and Lewington, 1998; Chambers *et al*., 2000). Its effect appears to depend upon its direct toxicity for endothelial cells. Endothelial dysfunction is associated with atherogenesis and oxidative stress in humans. Some observational studies have reported that light–moderate alcohol intake is associated with lower plasma total homocysteine level (Ubbink *et al*., 1998; de Bree *et al*., 2001). However, it was recently reported that serum homocysteine increases even after moderate alcohol consumption in social drinkers (Bleich *et al*., 2001). Thus, the cardioprotective role of moderate alcohol consumption, particularly in relation to homocysteine, remains debatable and the concept of the 'French paradox' needs further investigation (Badawy, 2001).

*Increase in paraoxonase activity*

Recent studies have implicated paraoxonase in providing protection against LDL oxidation, thus affecting the risk of CHD in the general population (van der Gaag *et al*., 1999). The human serum HDL-linked paraoxonase enzyme limits LDL peroxidation by preventing transformation of LDL into biologically active atherogenic particles. Fasting paraoxonase activity was higher after intake of wine, beer, and spirits than after water consumption, but did not differ significantly between the three alcoholic beverages (van der Gaag *et al*., 1999). These findings and those from other recent studies (Durrington *et al*., 2001) suggest that increased serum paraoxonase may be one of the biological mechanisms underlying the reduced CHD risk in moderate alcohol consumers.

*Moderate alcohol consumption raises oestrogen levels*

Alcohol consumption may increase blood oestradiol levels in postmenopausal women who are on oestrogen replacement therapy, and this may increase the risk of breast cancer (Purohit, 1998). Moderate alcohol intake exerts a major influence not only on oestradiol, testosterone, and the estimate of aromatization of testosterone to oestradiol, but also on the oestrogen-responsive pituitary hormones in normal postmenopausal women (Gavaler *et al*., 1993). These findings suggest that moderate alcohol use is an important factor for postmenopausal oestrogen status and may offer a partial explanation for the reported protective effect of moderate alcohol consumption with respect to postmenopausal cardiovascular disease risk. However, there are data suggesting that the use of both alcohol and oestrogen may increase breast cancer risk more than the use of either agent alone (Ginsburg, 1999).

*Moderate alcohol consumption reduces stress*

Light–moderate drinkers have less depression in the presence of stress, than persons in other more extreme drinking categories. According to Lipton (1994), moderate alcohol use may serve as a proxy for a spectrum of generally moderate behaviours that either attenuate the effect of stress on depression or suppress the effects of stress. A review of the literature (Baum-Baicker, 1985) on the positive psychological benefits of light and moderate alcohol consumption suggests that alcohol in moderate amounts is effective in reducing stress. Low and moderate doses of alcohol increase overall affective expression, happiness, euphoria, conviviality and pleasant and carefree feelings (Vasse *et al*., 1998). Tension, depression and self-consciousness have been reported to decrease with equal doses. Low alcohol doses have been found to improve certain types of cognitive performance. Included here are problem-solving and short-term memory (Baum-Baicker, 1985). Heavy drinkers and abstainers have higher rates of clinical depression than do regular moderate drinkers. Alcohol in low and moderate doses has been effective in the treatment of geropsychiatric problems (Baum-Baicker, 1985).

## GENERAL CONCLUSIONS AND COMMENTS

The putative health benefits of light–moderate alcohol drinking may vary among individuals. While the association between light–moderate drinking and reduced risk of CHD mortality is well established, the issues of causality and magnitude of effect are more problematic. A wide range of confounding factors may indirectly explain the apparent variability in cardiovascular benefits of light–moderate drinking. Published findings have, nevertheless, shown that alcohol's beneficial effects are independent of dietary and other known risk factors for heart disease, such as smoking and obesity.

Epidemiological studies have shown that the cardioprotective effect of alcohol does not include men aged <40 years or premenopausal women (Meister *et al*., 2000). There is also some evidence that the cardioprotective effect cannot be achieved if a person waits to reach middle age before starting to drink (Wannamethee and Shaper, 2002). Moreover, the putative benefit could be inflated because of the use of reference groups with different lifestyles and health profiles (Shaper and Wannamethee, 2000). Alcohol drinking patterns (occasional, regular, binge, with or without food, etc.) are also of importance in relation to the effects of intake.

Despite the overwhelming epidemiological evidence of an inverse relationship between moderate alcohol consumption and CHD, there remains a pending question. Is alcohol the direct cause of the observed cardioprotective effects or is it due to some other factors. Alcohol may directly increase the hepatic production and secretion of apolipoproteins and lipoprotein particles, increase triglyceride lipase concentrations, and decrease removal of circulating HDL-cholesterol. It appears that about half the apparent protective effect of alcohol against CHD is due to higher HDL-cholesterol, leading to an enhancement of reverse cholesterol transport, thereby reducing the risk of CHD (Goldberg and Soleas, 2001). In addition, alcohol may inhibit blood clotting and platelet aggregation, perhaps due to the presence of polyphenolic antioxidants in alcoholic beverages, partcularly in wine. Type of alcoholic beverage intake may play a role in the effects on CHD. Red wine has been shown *ex vivo* to inhibit low-density lipoprotein oxidation, increase antioxidant capacity in humans, and reduce

susceptibility of human plasma to lipid peroxidation. The non-alcoholic fraction of wine, represented mainly by phenolic compounds, may be the primary factor responsible for this protective effect.

Those who do not benefit from alcohol could have an even lower risk if they do not drink, because of the elevation by alcohol of the cardiovascular risk substance homocysteine. Though most of the evidence points to increased homocysteine after alcohol drinking (Bleich *et al*., 2001), an inverse relationship between moderate alcohol consumption and plasma total homocysteine levels has been observed in other studies, at least in men (Ubbink *et al*., 1998; de Bree *et al*., 2001; Ueland *et al*., 2001). In particular, serum homocysteine increased after moderate consumption of red wine and spirits, but not after moderate consumption of beer (van der Gaag *et al*., 2000). Vitamin $B_6$, vitamin $B_2$ and folate present in beer seem to prevent an alcohol-induced rise in serum homocysteine (de Bree *et al*., 2001; Mayer *et al*., 2001).

Taken together, in comparison with non-drinkers, individuals who consume light–moderate amounts of alcohol have, on average, lower death rates due to cardiovascular disorders. However, it is suggested that individuals who are currently non-drinkers should not be encouraged to start drinking alcohol because of its putative cardioprotective properties.

*Acknowledgements* — Financial support from the Volkswagen Foundation, Hannover, Germany is gratefully acknowledged.

## REFERENCES


Agarwal, D. P. and Seitz, H. K. (2001) *Alcohol in Health and Disease*. Marcel Dekker, New York.

Agarwal, D. P. and Srivastava, L. M. (2001) Does moderate alcohol intake protect against coronary heart disease? *Indian Heart Journal* **53**, 224–230.

Andreasson, S. (1998) Alcohol and J-shaped curves. *Alcoholism: Clinical and Experimental Research* **22**, 359S–364S.

Badawy, A. A.-B. (2001) Moderate alcohol consumption as a cardiovascular risk factor: the role of homocysteine and the need to re-explain the 'French Paradox'. *Alcohol and Alcoholism* **36**, 185–188.

Baum-Baicker, C. (1985) The psychological benefits of moderate alcohol consumption: a review of the literature. *Drug and Alcohol Dependence* **15**, 305–322.

Bell, R. A., Mayer-Davis, E. J., Martin, M. A., D'Agostino, R. B., Jr and Haffner, S. M. (2000) Associations between alcohol consumption and insulin sensitivity and cardiovascular disease risk factors: the Insulin Resistance and Atherosclerosis Study. *Diabetes Care* **23**, 1630–1636.

Beilin, L. J., Puddey, I. B. and Burke, V. (1996) Alcohol and hypertension — kill or cure? *Journal of Human Hypertension* **10** (Suppl. 2), S1–S5.

Berger, K., Ajani, U. A., Kase, C. S., Gaziano, J. M., Buring, J. E., Glynn, R. J. and Hennekens, C. H. (1999) Light-to-moderate alcohol consumption and risk of stroke among U.S. male physicians. *New England Journal of Medicine* **341**, 1557–1564.

Bleich, S., Bleich, K., Kropp, S., Bittermann, H. J., Degner, D., Sperling, W., Ruther, E. and Kornhuber, J. (2001) Moderate alcohol consumption in social drinkers raises plasma homocysteine levels: a contradiction to the 'French Paradox'? *Alcohol and Alcoholism* **36**, 189–192.

Castilho, L. N., Oliveira, H. C., Cazita, P. M., de Oliveira, A. C., Sesso, A. and Quintao, E. C. (2001) Oxidation of LDL enhances the cholesteryl ester transfer protein (CETP)-mediated cholesteryl ester transfer rate to HDL, bringing on a diminished net transfer of cholesteryl ester from HDL to oxidized LDL. *Clinica Chimica Acta* **304**, 99–106.

Chambers, J. C., Obeid, O. A., Refsum, H., Ueland, P., Hackett, D., Hooper, J., Turner, R. M., Thompson, S. G. and Kooner, J. S. (2000) Plasma homocysteine concentrations and risk of coronary heart disease in UK Indian Asian and European men. *Lancet* **355**, 523–527.

Corrao, G., Rubbiati, L., Bagnardi, V., Zambon, A. and Poikolainen, K. (2000) Alcohol and coronary heart disease: a meta-analysis. *Addiction* **95**, 1505–1523.

Criqui, M. (2001) Alcohol, lipoproteins and the French paradox. In *Alcohol in Health and Disease*, Agarwal, D. P. and Seitz, H. K. eds, pp. 597–609. Marcel Dekker, New York.

Danesh, J. and Lewington, S. (1998) Plasma homocysteine and coronary heart disease: systematic review of published epidemiological studies. *Journal of Cardiovascular Risk* **5**, 229–232.

de Bree, A., Verschuren, W. M., Blom, H. J. and Kromhout, D. (2001) Lifestyle factors and plasma homocysteine concentrations in a general population sample. *American Journal of Epidemiology* **154**, 150–154.

De Oliveira, E., Silva, E. R., Foster, D., McGee Harper, M., Seidman, C. E., Smith, J. D., Breslow, J. L. and Brinton, E. A. (2000) Alcohol consumption raises HDL cholesterol levels by increasing the transport rate of apolipoproteins A-I and A-II. *Circulation* **102**, 2347–2352.

Djousse, L., Pankow, J. S., Arnett, D. K., Zhang, Y., Hong, Y., Province, M. A. and Ellison, R. C. (2000) Alcohol consumption and plasminogen activator inhibitor type 1, the National Heart, Lung, and Blood Institute Family Heart Study. *American Heart Journal* **139**, 704–709.

Doll, R. (1997) One for the heart. *British Medical Journal* **315**, 1664–1668.

Dufour, M. C. (1999) What is moderate drinking? Defining 'drinks' and drinking levels. *Alcohol Research and Health* **23**, 5–14.

Durrington, P. N., Mackness, B. and Mackness, M. I. (2001) Paraoxonase and atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology* **21**, 473–480.

Facchini, F., Chen, Y. D. and Reaven, G. M. (1994) Light-to-moderate alcohol intake is associated with enhanced insulin sensitivity. *Diabetes Care* **17**, 115–119.

Flanagan, D. E., Moore, V. M., Godsland, I. F., Cockington, R. A., Robinson, J. S. and Phillips, D. I. (2000) Alcohol consumption and insulin resistance in young adults. *European Journal of Clinical Investigation* **30**, 297–301.

Fontana, P., Mooser, V., Bovet, P., Shamlaye, C., Burnand, B., Lenain, V., Marcovina, S. M., Riesen, W. and Darioli, R. (1999) Dose dependent inverse relationship between alcohol consumption and serum Lp(a) levels in black African males. *Arteriosclerosis, Thrombosis, and Vascular Biology* **19**, 1075–1082.

Gavaler, J. S., Deal, S. R., Van Thiel, D. H., Arria, A. and Allan, M. J. (1993) Alcohol and estrogen levels in postmenopausal women, the spectrum of effect. *Alcoholism: Clinical and Experimental Research* **17**, 786–790.

Gaziano, J. M., Gaziano, T. A., Glynn, R. J., Sesso, H. D., Ajani, U. A. and Stampfer, M. J. (2000) Light-to-moderate alcohol consumption and mortality in the Physicians' Health Study enrollment cohort. *Journal of the American College of Cardiology* **35**, 96–105.

Gillman, M. W., Cook, N. R., Evans, D. A., Rosner, B. and Hennekens, C. H. (1995) Relationship of alcohol intake with blood pressure in young adults. *Hypertension* **25**, 1106–1110.

Ginsburg, E. S. (1999) Estrogen, alcohol and breast cancer risk. *Journal of Steroid Biochemistry and Molecular Biology* **69**, 299–306.

Goldberg, D. M. and Soleas, G. J. (2001) Beverage alcohol consumption as a negative risk factor for coronary heart disease, biochemical mechanisms. In *Alcohol in Health and Disease*, Agarwal, D. P. and Seitz, H. K. eds, pp. 547–572. Marcel Dekker, New York.

Goldberg, D. M., Hoffman, B., Yang, J. and Soleas, G. J. (1999) Phenolic constituents, furans, and total antioxidant status of distilled spirits. *Journal of Agriculture and Food Chemistry* **47**, 3978–3985.

Griffin, B. A. (1999) Lipoprotein atherogenicity, an overview of current mechanisms. *Proceedings of the Nutrition Society* **58**, 163–169.

Grobbee, D. E., Rimm, E. B., Keil, U. and Renaud, S. (1999) Alcohol and the cardiovascular system. In *Health Issues Related to Alcohol*

*Consumption*, Macdonald, I. ed., pp. 125–179. Blackwell Science, London.
Gronbaek, M., Deis, A., Sorensen, T. I., Becker, U., Schnohr, P. and Jensen, G. (1999) Mortality associated with moderate intakes of wine, beer, or spirits. *British Medical Journal* **310**, 1165–1169.
Hannuksela, M. L. and Savolainen, M. J. (2001) Regulation of the quantity and quality of high density lipoproteins (HDL) by alcohol. In *Alcohol in Health and Disease*, Agarwal, D. P. and Seitz, H. K. eds, pp. 573–595. Marcel Dekker, New York.
Hendriks, H. F. and van der Gaag, M. S. (1998) Alcohol, coagulation and fibrinolysis. *Novartis Foundation Symposium* **216**, 111–120.
Kalant, H. and Poikolainen, K. (1999) Moderate drinking, concepts, definitions and public health significance. In *Health Issues Related to Alcohol Consumption*, Macdonald, I. ed., pp. 1–25. Blackwell Science, London.
Kervinen, K., Savolainen, M. J. and Kesaniemi, Y. A. (1993) Lp(a) levels increase after ethanol withdrawal. *Alcoholism: Clinical and Experimental Research* **17**, 926.
Kiechl, S., Willeit, J., Poewe, W., Egger, G., Oberhollenzer, F., Muggeo, M. and Bonora, E. (1996) Insulin sensitivity and regular alcohol consumption: A large, prospective, cross sectional population study (Bruneck study). *British Medical Journal* **313**, 1040–1044.
Klatsky, A. L. (2001) Alcohol and cardiovascular diseases. In *Alcohol in Health and Disease*. Agarwal, D. P. and Seitz, H. K. eds, pp. 517–546. Marcel Dekker, New York.
Krause, B. R. and Auerbach, B. J. (2001) Reverse cholesterol transport and future pharmacological approaches to the treatment of atherosclerosis. *Current Opinion in Investigative Drugs* **2**, 375–381.
Lacoste, L., Hung, J. and Lam, J. Y. (2001) Acute and delayed antithrombotic effects of alcohol in humans. *American Journal of Cardiology* **87**, 82–85.
Lazarus, R., Sparrow, D. and Weiss, S. T. (1997) Alcohol intake and insulin levels. The Normative Aging Study. *American Journal of Epidemiology* **145**, 909–916.
Leighton, F., Castro, C., Barriga, C. and Urquiaga, E. I. (1997) Wine and health. Epidemiological studies and possible mechanisms of the protective effects. *Reviews in Medicine Chile* **125**, 483–491.
Lipton, R. I. (1994) The effect of moderate alcohol use on the relationship between stress and depression. *American Journal of Public Health* **84**, 1913–1917.
Makela, P., Valkonen, T. and Poikolainen, K. (1997) Estimated numbers of deaths from coronary heart disease 'caused' and 'prevented' by alcohol: an example from Finland. *Journal of Studies on Alcohol* **58**, 455–463.
Marques-Vidal, P., Arveiler, D., Evans, A., Amouyel, P., Ferrieres, J. and Ducimetiere, P. (2001) Different alcohol drinking and blood pressure relationships in France and Northern Ireland: The PRIME Study. *Hypertension* **38**, 1361–1366.
Mayer, O., Jr, Simon, J. and Rosolova, H. (2001) A population study of the influence of beer consumption on folate and homocysteine concentrations. *European Journal of Clinical Nutrition* **55**, 605–609.
McCarty, M. F. (2001) Does regular ethanol consumption promote insulin sensitivity and leanness by stimulating AMP-activated protein kinase? *Medical Hypotheses* **57**, 405–407.
McElduff, P. and Dobson, A. J. (1997) How much alcohol and how often? Population based case–control study of alcohol consumption and risk of a major coronary event. *British Medical Journal* **314**, 1159–1164.
McKee, M. and Britton, A. (1998) The positive relationship between alcohol and heart disease in eastern Europe: potential physiological mechanisms. *Journal of the Research Society of Medicine* **91**, 402–407.
Mennen, L. I., Balkau, B., Vol, S., Cacès, E. and Eschwège, E. (1999) Fibrinogen, a possible link between alcohol consumption and cardiovascular disease? DESIR Study Group. *Arteriosclerosis, Thrombosis, and Vascular Biology* **19**, 887–892.
Meister, K. A., Whelan, E. M. and Kava, R. (2000) The health effects of moderate alcohol intake in humans: an epidemiologic review. *Critical Reviews in Clinical and Laboratory Sciences* **37**, 261–296.
Mukamal, K. J., Jadhav, P. P., D'Agostino, R. B., Massaro, J. M., Mittleman, M. A., Lipinska, I., Sutherland, P. A., Matheney, T., Levy, D., Wilson, P. W., Ellison, R. C., Silbershatz, H., Muller, J. E. and Tofler, G. H. (2001) Alcohol consumption and hemostatic factors, analysis of the Framingham Offspring cohort. *Circulation* **104**, 1367–1373.
Paassilta, M., Kervinen, K., Rantala, A. O., Savolainen, M. J., Lilja, M., Reunanen, A. and Kesaniemi, Y. A. (1998) Social alcohol consumption and low Lp(a) lipoprotein concentrations in middle aged Finnish men: population based study. *British Medical Journal* **316**, 594–595.
Puddey, I. B. and Croft, K. D. (1999) Alcohol, stroke and coronary heart disease. Are there anti-oxidants and pro-oxidants in alcoholic beverages that might influence the development of atherosclerotic cardiovascular disease? *Neuroepidemiology* **18**, 292–302.
Puddey, I. B., Croft, K. D., Abu-Amsha Caccetta, R. and Beilin, L. J. (1998) Alcohol, free radicals and antioxidants. *Novartis Foundation Symposium* **216**, 51–67.
Puddey, I. B., Rakic, V., Dimmitt, S. B. and Beilin, L. J. (1999) Influence of pattern of drinking on cardiovascular disease and cardiovascular risk factors — a review. *Addiction* **94**, 649–663.
Purohit, V. (1998) Moderate alcohol consumption and estrogen levels in postmenopausal women: a review. *Alcoholism: Clinical and Experimental Research* **22**, 994–997.
Rimm, E. B., Williams, P., Fosher, K., Criqui, M. and Stampfer, M. J. (1999) Moderate alcohol intake and lower risk of coronary heart disease, meta-analysis of effects on lipids and haemostatic factor. *British Medical Journal* **319**, 1523–1528.
Rotondo, S., Di Castelnuovo, A. and de Gaetano, G. (2001) The relationship between wine consumption and cardiovascular risk, from epidemiological evidence to biological plausibility. *Italian Heart Journal* **2**, 1–8.
Ruf, J. C. (1999) Wine and polyphenols related to platelet aggregation and atherothrombosis. *Drugs: Experimental and Clinical Research* **25**, 125–131.
San Jose, B., van de Mheen, H., van Oers, J. A., van Oers, J. A., Mackenbach, J. P. and Garretsen, H. F. (1999) The U-shaped curve, various health measures and alcohol drinking patterns. *Journal of Studies on Alcohol* **60**, 725–731.
Serafini, M., Laranjinha, J. A., Almeida, L. M. and Maiani, G. (2000) Inhibition of human LDL lipid peroxidation by phenol-rich beverages and their impact on plasma total antioxidant capacity in humans. *Journal of Nutritional Biochemistry* **11**, 585–590.
Shaper, A. G., Wannamethee, S. G. (2000) Alcohol intake and mortality in middle aged men with diagnosed coronary heart disease. *Heart* **83**, 394–399.
Sillanaukee, P., Koivula, T., Jokela, H., Pitkajarvi, T. and Seppa, K. (2000) Alcohol consumption and its relation to lipid-based cardiovascular risk factors among middle-aged women, the role of HDL(3) cholesterol. *Atherosclerosis* **152**, 503–510.
Srivastava, L. M., Vasisht, S., Agarwal, D. P. and Goedde, H. W. (1994) Relation between alcohol intake, lipoproteins and coronary heart disease: the interest continues. *Alcohol and Alcoholism* **29**, 11–24.
Testa, R. and Marcovina, S. M. (1999) The rate of plasmin formation after in vitro clotting is inversely related to lipoprotein(a) plasma levels. *International Journal of Clinical and Laboratory Research* **29**, 128–132.
Ubbink, J. B., Fehily, A. M., Pickering, J., Elwood, P. C. and Vermaak, W. J. (1998) Homocysteine and ischaemic heart disease in the Caerphilly cohort. *Atherosclerosis* **140**, 349–356.
Ueland, P. M., Nygard, O., Vollset, S. E. and Refsum, H. (2001) The Hordaland Homocysteine Studies. *Lipids* **36** (Suppl.), S33–S39.
van de Wiel, A., van Golde, P. M., Kraaijenhagen, R. J., von dem Borne, P. A., Bouma, B. N. and Hart, H. C. (2001) Acute inhibitory effect of alcohol on fibrinolysis. *European Journal of Clinical Investigation* **31**, 164–170.
van der Gaag, M. S., van Tol, A., Scheek, L. M., James, R. W., Urgert, R., Schaafsma, G. and Hendriks, H. F. (1999) Daily moderate alcohol consumption increases serum paraoxonase activity, a diet controlled randomised intervention study in middle aged men. *Atherosclerosis* **147**, 405–410.
van der Gaag, M. S., Ubbink, J. B., Sillanaukee, P., Nikkari, S. and Hendriks, H. F. (2000) Effect of consumption of red wine, spirits, and beer on serum homocysteine. *Lancet* **355**, 1522.
van Golde, P. H., Sloots, L. M., Vermeulen, W. P., Wielders, J. P., Hart, H. C., Bouma, B. N. and van de Wiel, A. (1999) The role of alcohol in the anti low density lipoprotein oxidation activity of red wine. *Atherosclerosis* **147**, 365–370.

van Tol, A. and Hendriks, H. F. (2001) Moderate alcohol consumption, effects on lipids and cardiovascular disease risk. *Current Opinion in Lipidology* **12**, 19–23.

Vasisht, S., Agarwal, D. P., Wasir, H. S. and Srivastava, L. M. (1996) Lipoprotein(a) levels in alcohol drinking and alcohol non-drinking coronary artery disease patients. *Indian Journal of Clinical Biochemistry* **11**, 176–179.

Vasse, R. M., Nijhuis, F. J. and Kok, G. (1998) Associations between work stress, alcohol consumption and sickness absence. *Addiction* **93**, 231–241.

Wannamethee, S. G. and Shaper, A. G. (2002) Taking up regular drinking in middle age: effect on major coronary heart disease events and mortality. *Heart* **87**, 32–36.