Moderate alcohol consumption: effects on lipids and cardiovascular disease risk

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Light to moderate alcohol consumption is associated with a reduced risk of coronary heart disease, as well as ischaemic stroke and possibly type 2 diabetes. Epidemiological and physiological data are in favour of a causal relationship. Proposed protective mechanisms include the stimulation of HDL-mediated processes such as reverse cholesterol transport and antioxidative effects. More well-controlled studies are needed to provide a complete understanding of the complexity of the underlying physiological mechanisms. Curr Opin Lipidol 12:19–23. © 2001 Lippincott Williams & Wilkins.

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Abbreviation

LCAT lecithin : cholesterol acyltransferase

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Introduction

The devastating effects of alcohol abuse on social and physiological well-being have been known for a long time. However, positive effects of moderate alcohol consumption have also gained attention during the past decade. It is well established now that light to moderate alcohol consumption is associated with a reduced risk of coronary heart disease. Other cardiovascular diseases are also beneficially affected. Epidemiological studies indicate that approximately 50% of the benefit may originate from an increase in plasma HDL cholesterol concentrations.

About 5 years ago a review of the effects of alcohol on lipoproteins was published in this journal [1]. Since then our knowledge of this topic has expanded and more detailed analyses of the association between alcohol consumption and cardiovascular disease risk have been performed. During the past few years new protective mechanisms have been proposed. Conflicting results have been reported on the effects of specific beverage types. These topics are presented and discussed in this review, which focuses on the effects of moderate alcohol consumption.

Coronary artery disease risk

Epidemiological studies describing the relationship between alcohol consumption and the cardiovascular system have recently been summarized [2••]. Some of the main conclusions are that light to moderate drinking is associated with a reduced risk of the development of coronary heart disease in middle-aged and elderly men and women living in Western countries, and that it is highly likely that the association is causal. Recent studies [3,4] have also shown a similar association in non-Western populations. Moderate alcohol consumption could also protect after a first myocardial infarction [5].

Over the past years the balance between benefits and adverse health effects has often been discussed, and the effects of alcohol consumption on overall mortality have been investigated in depth. Gaziano *et al.* [6] recently confirmed the U-shaped relationship between alcohol consumption and total mortality described previously [7–10]. The reduction in total mortality results mostly from the reduction of cardiovascular diseases. The description of the overall disease burden caused by alcohol consumption allows for the definition of that quantity of alcohol that is associated with the lowest mortality (nadir). The nadir appears to vary substantially between

countries (US men: 69 g per week; UK men: 116 g per week) and between the sexes (US women: 26 g per week), but is not affected by age [11•]. This was shown in a systematic review of 20 cohort studies with a total of more than 60 000 deaths in men and almost 75 000 deaths in women.

The inverse relationship between moderate alcohol consumption and coronary heart disease has now been studied both in men and women [12–17]. Benefits for women are mostly found at lower quantities of alcohol, and appear to be most pronounced in postmenopausal women. This is not surprising because this age group, like men over the age of 50 years, has a marked increase in cardiovascular risk.

Some reports have suggested that the beverage type may be important [8,17], an issue that is extensively discussed in a comprehensive review [18] of the effect of specific beverages on coronary heart disease risk. The latter study showed that observational studies, including only those that provide specific information on the consumption of beer, wine and spirits in relation to the risk of coronary heart disease, indicate that moderate consumption of all three alcohol-containing beverages is linked with a lower risk. A substantial portion of the benefit is thus connected with the alcohol component, rather than with specific non-alcohol components present in the different types of beverages.

Stroke and heart failure

It has become clear that other cardiovascular diseases and diseases with an aetiology associated with peripheral arteries may also be affected by alcohol consumption. Light to moderate drinking is associated with a lower incidence of ischaemic stroke [2••,19,20], whereas binge drinking on the other hand is associated with an increased risk of haemorrhagic as well as ischaemic stroke [2••,21–24]. Arrythmias are associated with heavy alcohol consumption, even in men without cardiovascular disease [25]. The incidence of sudden cardiac death may also be increased after heavy alcohol consumption [26,27], but decreased with light to moderate drinking [28].

Type 2 diabetes mellitus

The results from recent studies on the association between alcohol consumption, insulin resistance and type 2 diabetes mellitus are very interesting. Resistance to the metabolic actions of insulin is not only associated with type 2 diabetes, but also plays an important role in the pathogenesis of obesity and cardiovascular diseases. Flanagan *et al.* [29•] confirmed earlier studies by showing a positive correlation between insulin sensitivity and alcohol consumption in young adults, independent of gender. These data raise the possibility of a putative protective role of moderate alcohol consumption in the development of type 2 diabetes [30–33]. Also, moderate alcohol consumption could have an overall beneficial effect on the risk of death caused by coronary heart disease in people with type 2 diabetes [34,35].

Dementia

Risk factors for vascular disease and stroke may be associated with cognitive impairment and dementia [36]. It is interesting to explore further the effects of moderate alcohol consumption on cognitive performance, Alzheimer's disease and dementia [37–40].

Physiological mechanisms of moderate alcohol consumption related to cardiovascular disease

It is important to examine the physiological changes occurring after moderate alcohol consumption in order to obtain a better understanding of how disease aetiology may be altered. However, well-controlled studies in humans describing these physiological changes are still scarce.

A meta-analysis was recently published of all experimental studies that assessed the effects of moderate alcohol intake on lipids and haemostatic factors [41•]. Increases in HDL cholesterol, apolipoprotein AI and total plasma triglycerides were quantified for an experimental dose of 30 g alcohol per day. On the basis of published associations between these biomarkers and risk, this dose was estimated to reduce the risk of coronary heart disease by approximately 25%. This percentage is comparable to the relative risks reported in several large-scale prospective studies [42–44]. Altogether, these data strongly suggest that alcohol consumption may be causally related to a lower risk of coronary heart disease [41•].

Lipid and lipoprotein metabolism is affected by alcohol consumption in several ways. It was recently quantitated how a moderate dose of alcohol (24 g) affects hepatic lipid metabolism. Using sophisticated techniques, Siler *et al.* [45•] confirmed and quantitated that the bulk of a moderate dose of alcohol is metabolized to acetate. Only a minor portion ($<5\%$) is used for the de-novo synthesis of fatty acids. The acetate produced is released into the circulation [45•] and may inhibit whole body lipid and carbohydrate oxidation.

Moderate alcohol consumption, which leads to inhibition of the Krebs cycle, may inhibit hepatic fatty acid oxidation, resulting in a stimulation of triglyceride synthesis. The triglycerides are secreted in VLDL. In healthy normolipidaemic individuals this does not lead to elevated fasting plasma triglycerides, probably because of a compensatory increase in lipoprotein lipase

activity. Increased VLDL turnover contributes to the formation of HDL precursors and thus results in elevated plasma HDL concentrations [46]. Interestingly, fasting plasma VLDL levels are hardly affected by alcohol consumption, but a moderate dose of alcohol consumed in combination with a meal transiently increases plasma triacylglycerol concentrations [47] and decreases plasma LDL cholesterol [48]. This postprandial hypertriglyceridaemia after moderate alcohol consumption also profoundly affects the chemical composition of HDL [47,49]. HDL triglycerides are elevated directly after the fat-containing meal, whereas HDL phospholipids are elevated several hours later [50].

Fasting plasma HDL cholesterol is clearly increased during moderate alcohol consumption [49]. Not only HDL lipids are changed by alcohol consumption. Studies in healthy volunteers have shown that moderate alcohol consumption also increases plasma HDL apolipoproteins, lecithin : cholesterol acyltransferase (LCAT) and phospholipid transfer protein activity levels [49]. It is likely that the rates of formation of plasma HDL apolipoproteins, HDL-phospholipids and HDL-cholesteryl esters are all increased, resulting in an elevation of the number of HDL particles per volume of plasma. In the fasting state, plasma cholesteryl ester transfer by cholesteryl ester transfer protein is not influenced by moderate alcohol consumption, as a result of normal plasma VLDL levels and unaffected cholesteryl ester transfer protein concentration [51]. However, net mass cholesteryl ester transfer is increased during alcohol consumption with dinner [47].

High-density lipoprotein functions and disease

Because moderate alcohol consumption is associated with coronary artery disease mainly via its HDL raising effects, it is crucial to study the functional consequences of this increase in plasma HDL concentration and of the effects on HDL composition. Several properties of HDL may be important.

High-density lipoprotein and reverse cholesterol transport

An important property of HDL is its capacity to take up excess cholesterol from peripheral cells and transport it to the liver for excretion and degradation to bile acids. Two mechanisms may be important in cholesterol efflux [52••]. First, cholesterol may be desorbed from the plasma membrane to phospholipid-rich acceptors like HDL. Second, cellular cholesterol (and phospholipid) efflux may be facilitated by the ABC-1 protein, directing the cholesterol and phospholipids to lipid-poor pre-β-HDL particles. The resulting lipoprotein particles are substrates for LCAT, which synthesizes cholesteryl esters from the unesterified cholesterol of cellular origin. Changes in lipoprotein metabolism allow for each of these mechanisms to be stimulated by moderate alcohol consumption: (i) via the HDL raising mechanisms described in the paragraph above; and (ii) via an increase in HDL-associated activities of enzymes such as paraoxonase-1, LCAT and phospholipid transfer protein [49]. Only limited data are available on the effects of moderate alcohol consumption on cellular cholesterol efflux [53]. Unpublished data from our laboratory show that moderate alcohol consumption, either as beer, wine or spirits, increases the capacity of plasma to stimulate cholesterol efflux from Fu5AH cells (van der Gaag, *et al.*, unpublished data).

High-density lipoprotein as an antioxidant

A good antioxidant status is important for human health. Low plasma levels of antioxidants as well as low intakes of dietary antioxidants have been associated with an increased risk of atherosclerotic disease in epidemiological studies. However, intervention studies have been less convincing [54].

Alcohol abuse results in increased urinary lipid peroxides, indicating oxidative stress [55]. Red wine consumption has received much attention as a potential factor improving the antioxdant status [56–58]. Increases in plasma antioxidant concentrations after the consumption of red wine may [59,60], or may not [61] occur. It is unlikely, however, that the phenolic acids present in red wine, after the consumption of moderate amounts, are able to raise the plasma levels enough to protect lipoproteins from oxidative modification. Ex-vivo lipoprotein oxidation is also not inhibited by these compounds [59].

Alternatively, we have shown that the activity of paraoxonase-1 is increased by 8% after drinking moderate amounts of beer, wine or spirits [62]. Paraoxonase-1 is associated with HDL and potently inhibits LDL modification *in vivo* by the degradation of oxidized phospholipids. Paraoxonase-1 activity may also protect human aortic endothelial cells against monocyte adhesion induced by mildly oxidized LDL [63]. By these paraoxonase-1-related mechanisms, the consumption of moderate amounts of alcohol, rather than the intake of non-alcohol components contained in alcoholic beverages, could mediate antioxidant activity *in vivo*.

Alcohol effects not mediated by high-density lipoproteins

Moderate alcohol consumption may not only protect via HDL, but probably also via a whole range of other mechanisms. These include effects on LDL [48], haemostasis and endothelium-dependent functioning of the vascular wall (vasodilation).

Haemostasis

Coronary thrombosis is the final result of plaque instability, involving an imbalance between clotting and fibrinolysis. Platelet aggregation is a primary trigger for myocardial infarction. The acute effects of alcohol on platelet aggregation are conflicting, but daily moderate alcohol consumption may cause decreased platelet aggregability after a few weeks [64]. This is based mainly on the inverse correlation between alcohol intake and platelet aggregation reported earlier [65].

Many, but not all studies, have found an inverse correlation between fibrinogen levels (a precursor protein of fibrin, a main constituent of blood clots) and alcohol use [64]. Fibrinolytic activity, which plays a crucial role in the ability to prevent and dissolve clots, is acutely increased by alcohol consumption [66,67].

Vascular wall functioning

Studies on the effects of moderate alcohol consumption on vascular wall functioning are still rare. It was recently reported that 3 ml of red wine/kg body weight (approximately two drinks), taken with a high-fat meal, does not affect flow-mediated dilation of the brachial artery [68]. Another group reported decreased flow-mediated dilation after a longer-term high-fat diet. This decrease did not occur after supplementation with wine [69]. Also, coronary flow-velocity reserve may be improved by red wine [70]. Homocysteine, an independent coronary heart disease risk factor and regulator of the vascular wall, may be affected differently by moderate intakes of beer, wine or spirits. Recent data show that beer does not increase this parameter whereas wine and spirits do [71]. It is obvious that further studies are needed on this interesting topic.

Conclusion

Light to moderate alcohol consumption is associated with a reduced risk of coronary heart disease and some other diseases. The data strongly suggest a causal relationship. New protective mechanisms have been proposed. More well-controlled studies are needed to understand fully the complexity of the underlying physiological mechanisms.

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The authors dedicate this article to Martijn van der Gaag, a PhD student from our laboratory studying the physiological effects of moderate alcohol consumption on HDL composition and functioning. Martijn died in January 2000 at the age of 26. We lost an extremely kind colleague and an excellent scientist.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1 Savolainen MJ, Kesäniemi YA. Effects of alcohol on lipoproteins in relation to coronary heart disease. Curr Opin Lipidol 1995; 6:243–250.

2 •• Grobbee DE, Rimm EB, Keil U, Renaud S. Alcohol and the cardiovascular system. In: Health issues related to alcohol consumption, 2nd ed. McDonald I (editor). ILSI Europe: Blackwell Science; 1999. pp. 125–179.
In this excellent book all major health issues related to alcohol consumption are reviewed by experts in the field.

3 Yuan J-M, Ross RK, Gao Y-T, *et al.* Folow up study of moderate alcohol intake and mortality among middle-aged men in Shanghai, China. BMJ 1997; 314:18–23.

4 Kitamura A, Iso H, Sankai T, *et al.* Alcohol intake and premature coronary heart disease in urban Japanese men. Am J Epidemiol 1998; 147:59–65.

5 Muntwyler J, Hennekens CH, Buring JE, Gaziano JM. Mortality and light to moderate alcohol consumption after myocardial infarction. Lancet 1998; 352:1882–1885.

6 Gaziano JM, Gaziano TA, Glynn RJ, *et al.* Light-to-moderate alcohol consumption and mortality in the physicians' health study enrolment cohort. J Am Coll Cardiol 2000; 35:96–105.

7 Keil U, Chambless LE, Döring A, *et al.* The relation of alcohol intake to coronary heart disease and all-cause mortality in a beer-drinking population. Epidemiology 1997; 8:150–156.

8 Renaud SC, Gueguen R, Siest G, Salamon R. Wine, beer, and mortality in middle-aged men from eastern France. Arch Intern Med 1999; 159:1865–1870.

9 Renaud SC, Guéguen R, Schenker J, Houtaud A. Alcohol and mortality in middle-aged men from Eastern France. Epidemiology 1998; 9:184–188.

10 Camargo CA, Stampfer MJ, Glynn RJ, *et al.* Moderate alcohol consumption and risk for angina pectoris or myocardial infarction in US male physicians. Ann Intern Med 1997; 126:372–375.

11 • White IR. The level of alcohol consumption at which all-cause mortality is least. J Clin Epidemiol 1999; 52:967–975.
A valuable study illustrating heterogeneity between countries.

12 Fuchs CS, Stampfer MJ, Colditz GA, *et al.* Alcohol consumption and mortality among women. N Engl J Med 1995; 332:1245–1250.

13 Nanchahal K, Ashton WD, Wood DA. Alcohol consumption, metabolic cardiovascular risk factors and hypertension in women. Int J Epidemiol 2000; 29:57–64.

14 Thun MJ, Peto R, Lopez AD, *et al.* Alcohol consumption and mortality among middle-aged and elderly US adults. N Engl J Med 1997; 337:1705–1714.

15 Rehm JT, Bondy SJ, Sempos CT, Vuong CV. Alcohol consumption and coronary heart disease morbidity and mortality. Am J Epidemiol 1997; 146:495–501.

16 Klatsky AL, Armstrong MA, Friedman GD. Red wine, white wine, liquor, beer, and risk of coronary heart disease hospitalization. Am J Cardiol 1997; 80:416–420.

17 Grønbaek M, Deis A, Sorensen TIA, *et al.* Mortality associated with moderate intakes of wine, beer, or spirits. BMJ 1995; 310:1165–1169.

18 Rimm EB, Klatsky A, Grobbee D, Stampfer MJ. Review of moderate alcohol consumption and reduced risk of coronary heart disease: is the effect due to beer, wine, or spirits? BMJ 1996; 312:731–736.

19 Berger K, Ajani UA, Kase CS, *et al.* Light-to-moderate alcohol consumption and the risk of stroke among US male physicians. N Engl J Med 1999; 341:1557–1564.

20 Sacco RL, Elkind M, Boden-Albala B, *et al.* The protective effect of moderate alcohol consumption on ischemic stroke. JAMA 1999; 281:53–60.

21 Kiyohara Y, Kato I, Iwamoto H, *et al.* The impact of alcohol and hypertension on stroke incidence in a general Japanese population. Stroke 1995; 26:368–372.

22 Juvela S, Hillbom M, Palomäki H. Risk factors for spontaneous intracerebral hemorrhage. Stroke 1995; 26:1558–1564.

23 Hansagi H, Romelsjö A, Gerhardson de Verdier M, *et al.* Alcohol consumption and stroke mortality. 20 year follow-up of 15077 men and women. Stroke 1995; 26:1768–1673.

24 Hillbom M, Numminen H, Juvela S. Recent heavy drinking of alcohol and embolic stroke. Stroke 1999; 30:2307–2312.

25 Engstrom G, Hedblad B, Janzon L, Juul-Moller S. Ventricular arrhythmias during 24-h ambulatory ECG recording: incidence, risk factors and prognosis in men with and without a history of cardiovascular disease. J Intern Med 1999; 246:363–372.

26 Wannamethee G, Shaper AG. Alcohol and sudden cardiac death. Br Heart J 1992; 68:443–448.

27 Kadis P, Balazic J, Ferlan-Marolt V. Alcoholic ketoacidiosis: a cause of sudden death of chronic alcoholics. Forensic Sci Int 1999; 103:S53–S59.

28 Albert CM, Manson JE, Cook NR, *et al.* Moderate alcohol consumption and the risk of sudden cardiac death among US male physicians. Circulation 1999; 100:944–950.

29 • Flanagan DEH, Moore VM, Godsland IF, *et al.* Alcohol consumption and insulin resistance in young adults. Eur J Clin Invest 2000; 30:297–301.
A cross-sectional study in 154 young men and women showing a positive association between regular alcohol consumption and insulin sensitivity, independent of body mass index.

30 Stampfer MJ, Colditz GA, Willett WC, *et al.* A prospective study of moderate alcohol drinking and risk of diabetes in women. Am J Epidemiol 1988; 128:549–558.

31 Tsumura K, Hayashi T, Suematsu C, *et al.* Daily alcohol consumption and the risk of type 2 diabetes in Japanese men – The Osaka Health Survey. Diabetes Care 1999: 22:1432–1437.

32 Wei M, Kampert JB, Gibbons LW, *et al.* Alcohol intake and incidence of type 2 diabetes in men. Diabetes Care. 2000; 23:18–22.

33 Ajani UA, Hennekens CH, Spelsberg A, Manson JE. Alcohol consumption and risk of type 2 diabetes mellitus among US male physicians. Arch Intern Med 2000; 160:1025–1030.

34 Valmadrid CT, Klein R, Moss SE, *et al.* Alcohol intake and the risk of coronary heart disease mortality in persons with older-onset diabetes mellitus. JAMA 1999; 282:239–246.

35 Solomon CG, Hu FB, Stampfer MJ, *et al.* Moderate alcohol consumption and risk of coronary heart disease among women with type 2 diabetes mellitus. Circulation 2000; 102:494–499.

36 Breteler MMB, Bots ML, Ott A, Hofman A. Risk factors for vascular disease and dementia. Haemostasis 1998; 28:167–173.

37 Bates ME, Tracy JI. Cognitive functioning in young 'social drinkers'. Is there impairment to detect? J Abnorm Psychol 1990; 99:242–249.

38 Elias PK, Elias MF, D'Agostino RB, *et al.* Alcohol consumption and cognitive performance in the Framingham Heart Study. JAMA 1999; 150:580–589.

39 Orgogozo JM, Dartigues JF, Lafont S, *et al.* Wine consumption and dementia in the elderly: a prospective community study in the Bordeaux area. Rev Neurol 1997; 153:185–192.

40 Breteler MMB, Mehta K, Ott A, *et al.* Alcohol consumption and dementia [Abstract]. The Rotterdam Study. J Neurol 1997; 37:1295–1300.

41 • Rimm EB, Williams P, Fosher K, *et al.* Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors. BMJ 1999; 319:1523–1528.
A valuable study into the mechanisms of the protective effects of a moderate alcohol intake on the risk of coronary heart disease.

42 Klatsky AL. Epidemiology of coronary heart disease – influence of alcohol. Alcohol Clin Exp Res 1994; 18:88–96.

43 Rimm EB, Giovannuci EL, Willett WC, *et al.* A prospective study of alcohol consumption and the risk of coronary heart disease in men. Lancet 1991; 338:464–468.

44 Doll R, Peto R, Hall E, *et al.* Mortality in relation to consumption of alcohol: 13 years' observations on male British doctors. BMJ 1994; 309:911–918.

45 • Siler SQ, Nees RA, Hellerstein MK. De novo lipogenesis, lipid kinetics, and whole-body lipid balances in humans after acute alcohol consumption. Am J Clin Nutr 1999; 70:928–936.
An excellent study using sophisticated techniques to quantitate the metabolic effects of moderate alcohol consumption.

46 Taskinen M-R, Valimaki M, Nikkila EA, *et al.* Sequence of alcohol-induced initial changes in plasma lipoproteins (VLDL and HDL) and lipolytic enzymes in humans. Metabolism 1985; 34:112–119.

47 van Tol A, Groener JEM, Scheek LM, *et al.* Induction of net mass lipid transfer reactions in plasma by wine consumption with dinner. Eur J Clin Invest 1995; 25:390–395.

48 van Tol A, van der Gaag MS, Scheek LM, *et al.* Changes in postprandial lipoproteins of low and high density caused by moderate alcohol consumption with dinner [suppl 1]. Atherosclerosis 1998; 141:S101–S103.

49 van Tol A, van der Gaag MS, Scheek LM, *et al.* Moderate alcohol consumption with dinner increases phospholipid transfer and LCAT activity but decreases relative cholesteryl ester transfer. Abstract 70th EAS Congress, Geneva, Switzerland, 1998; p. 113.

50 Hendriks HFJ, Veenstra J, van Tol A, *et al.* Moderate doses of alcoholic beverages with dinner and postprandial high density lipoprotein composition. Alcohol Alcoholism 1998; 33:403–410.

51 Nishiwaki M, Ishikawa T, Ito T, *et al.* Effects of alcohol on lipoprotein lipase, hepatic lipase, cholesteryl ester transfer protein, and lecithin:cholesterol acyltransferase in high-density lipoprotein cholesterol elevation. Atherosclerosis 1994; 111:99–109.

52 •• Rothblat GH, de la Llera-Moya M, Atger V, *et al.* Cell cholesterol efflux: integration of old and new observations provides new insights. J Lipid Res 1999; 40:781–796.
An excellent review of the various mechanisms whereby cholesterol efflux may occur.

53 Senault C, Betoulle D, Luc G, *et al.* Beneficial effects of a moderate consumption of red wine on cellular cholesterol efflux in young men. Nutr Metab Cardiovasc Dis 2000; 10:63–69.

54 Gaziano JM. Antioxidant vitamins and cardiovascular disease. Proc Assoc Am Phys 1999; 111:2–9.

55 Meagher EA, Barry OP, Burke A, *et al.* Alcohol-induced generation of lipid peroxidation products in humans. J Clin Invest 1999; 104:805–813.

56 Kondo K, Matsumoto A, Kurata H, *et al.* Inhibition of oxidation of low-density lipoprotein with red wine. Lancet 1994; 344:1152.

57 Sharpe PC, McGrath LT, McClean E, *et al.* Effect of red wine consumption on lipoprotein 9a0 and other risk factors for atherosclerosis. Q J Med 1995; 88:101–108.

58 Cao G, Prior RL. Comparison of different analytical methods for assessing total antioxidant capacity of human serum. Clin Chem 1998; 44:1309–1315.

59 Caccetta RAA, Croft KD, Beilin LJ, Puddey IB. Ingestion of red wine significantly increases plasma phenolic acid concentrations but does not acutely affect ex vivo lipoprotein oxidizability. Am J Clin Nutr 2000; 71:67–74.

60 Bell JRC, Donovan JL, Wong R, *et al.* (+)-Catechin in human plasma after ingestion of a single serving of reconstituted red wine. Am J Clin Nutr 2000; 71:103–108.

61 van der Gaag MS, van den Berg R, van den Berg H, *et al.* Moderate consumption of beer, red wine and spirits has counteracting effects on plasma antioxidants in middle-aged men. Eur J Clin Invest 2000; 54:586–591.

62 van der Gaag MS, van Tol A, Scheek L, *et al.* Daily moderate alcohol consumption increases serum paraoxonase activity; a diet-controlled, randomised intervention study in middle-aged men. Atherosclerosis 1999; 147:405–410.

63 Watson AD, Berliner JA, Hama SY, *et al.* Protective effect of high density lipoprotein associated paraoxonase-inhibition of the biological activity of minimally oxidized low density lipoprotein. J Clin Invest 1995; 96:2882–2891.

64 Hendriks HFJ, van der Gaag MS. Alcohol, coagulation and fibrinolysis. In: Alcohol and cardiovascular diseases. (Novartis Foundation Symposium 216). Chichester: Wiley; 1998. pp. 111–124.

65 Renaud S, Beswick AD, Fehily AM, *et al.* Alcohol and platelet aggregation: the Caerphilly Protective Heart Disease Study. Am J Clin Nutr 1992; 55:1012–1017.

66 Hendriks HFJ, Veenstra J, Velthuis-te Wierik EJM, *et al.* Effect of moderate dose of alcohol with evening meal on fibrinolytic factors. BMJ 1994; 308:1003–1006.

67 Ridker PM, Vaughan DE, Stampfer MJ, *et al.* Association of moderate alcohol consumption and plasma concentration of endogenous tissue-type plasminogen activator. JAMA 1994; 272:929–933.

68 Djousse L, Ellison RC, McLennan CE, *et al.* Acute effects of a high-fat meal with and without red wine on endothelial function in healthy subjects. Am J Cardiol 1999; 84:660–664.

69 Cuevas AM, Guasch V, Castillo O, *et al.* A high-fat diet induces and red wine counteracts endothelial dysfunction in human volunteers. Lipids 2000; 35:143–148.

70 Shimada K, Watanabe H, Hosoda K, *et al.* Effect of red wine on coronary flow-velocity reserve. Lancet 1999; 354:1002.

71 van der Gaag MS, Ubbink JB, Sillanaukee P, *et al.* Effects of consumption of red wine, spirits, and beer on serum homocysteine. Lancet 2000; 355:1522.