

The positive relationship between alcohol and heart disease in eastern Europe: potential physiological mechanisms

Martin McKee MD FRCP Annie Britton MSc

J R Soc Med 1998;91:402-407

Research into the effect of alcohol on cardiovascular disease has indicated protective effects from moderate consumption. These observations, made in industrialized countries, have influenced policies on alcohol in countries where the situation may be quite different—specifically, where consumption is substantially higher or patterns of drinking are different. In central and eastern Europe and the former Soviet Union, a growing body of epidemiological research indicates a positive rather than negative association between alcohol consumption and cardiovascular deaths, especially sudden cardiac deaths. By means of a systematic review of published work, we examine whether there is a physiological basis for the observed association between alcohol and heart disease seen in eastern Europe, focusing on the effects of high levels of consumption and of irregular or binge drinking.

In binge drinkers, cardioprotective changes in high-density lipoproteins are not seen, and adverse changes in low-density lipoproteins are acquired. Irregular drinking is associated with an increased risk of thrombosis, occurring after cessation of drinking. It predisposes both to histological changes in the myocardium and conducting system and to a reduction in the threshold for ventricular fibrillation.

Measures of frequency as well as quantity of consumption should be included in epidemiological studies. Taken with the epidemiological evidence emerging from eastern Europe, these observations have important implications for estimates of the burden of disease attributable to alcohol.

INTRODUCTION

In 1985, Russian life expectancy at birth increased by 2 years within a single calendar year, largely because of a reduction in deaths from cardiovascular disease. This coincided with a major, and initially highly successful, campaign initiated by the newly appointed communist party general secretary, Michael Gorbachev, to reduce consumption of alcohol. Detailed examination of these events, and the subsequent fall in Russian life expectancy, provides considerable evidence that, in Russia, alcohol consumption is closely associated with deaths from heart disease. Specifically, there is a close association in the age, gender¹ and regional² pattern of cardiovascular and directly alcohol related deaths.

These findings appear at odds with the prevailing view in the west that alcohol, at least when consumed in moderate amounts, is cardioprotective. This is exemplified by the statement in the recent WHO/World Bank report on the global burden of disease that 'alcohol is cardio-protective at all levels of consumption'³. In particular, it appears incompatible with the low death rate from cardiovascular

disease in France, where official alcohol consumption figures are similar to those in Russia⁴. This apparent contradiction has contributed to the difficulty of developing an effective policy response in Russia, with many Russian authorities and some western commentators attributing much of the apparently alcohol related mortality in Russia to the quality of the product rather than to how much and in what ways it is consumed⁵.

There are, however, important cultural differences in drinking patterns. In countries such as France, alcohol is typically consumed as wine with meals, whereas in Russia it is much more likely to be drunk as spirits, in binges⁶ (defined as periods of abstinence interrupted by sessions at which large volumes are drunk).

How relevant to Russia is research undertaken in countries with different drinking cultures? Much of the work on cardiovascular effects of alcohol has concentrated on amount drunk and not drinking pattern. When exposure is defined simply according to the amount drunk in a defined period, typically a week, a cardioprotective effect of moderate drinking is consistently found⁷⁻⁹ with one important exception: a cohort study that included both American and Russian men and women showed a protective effect in Americans but not in Russians¹⁰. The authors were at a loss to explain this observation. In contrast, those few

European Centre on Health of Societies in Transition, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK

studies that have defined exposure in terms of its pattern or context, such as 'problem drinking'¹¹⁻¹³, frequency of hangovers¹⁴, or amount drunk at one time¹⁵, have equally consistently revealed an increased risk of cardiac death, especially sudden cardiac death. This work has, however, received much less attention.

A recent observation indicates the importance of resolving this apparent paradox. In Moscow, there is a significant increase in sudden cardiac death at weekends, most obvious among young and early middle-aged men¹⁶. This is strikingly similar to the pattern of deaths from alcohol poisoning and from accidents and violence. Although there may be some misclassification, especially as such deaths, by their nature, take place unobserved, there is evidence from necropsies that a substantial proportion are associated with specific histological changes of alcoholic damage to the myocardium¹⁷.

These findings raise the question of whether differences in the pattern of drinking have different physiological consequences and, specifically, whether a drinking culture characterized by binges can explain the observed pattern of cardiovascular deaths in eastern Europe. This paper addresses this question.

POSSIBLE MECHANISMS

If binge drinking is a cause of cardiovascular deaths there are potentially four main mechanisms. The first is an effect on lipids that, instead of reducing the risk of coronary artery disease, increases it. The second is an effect on clotting, which might increase the risk of thrombosis. The third is an effect on the myocardium or its conducting system, leading to a greater risk of arrhythmias. The fourth is an effect on blood pressure, causing either an acute increase or sustained hypertension. These have been examined by means of a systematic review of published work. MEDLINE was searched for the years 1966-1997 and EMBASE for the years 1980-1997 by use (in various combinations) of the thesaurus terms alcohol abuse, cardiovascular disease, sudden cardiac death, lipoproteins, cardiac arrhythmia, platelet aggregation, fibrinolysis, hypertension (each with all subheadings) and the words 'binge' and 'binging'. In addition, references cited in papers identified were obtained.

Lipids

Regular, moderate alcohol consumption is believed to exert its cardioprotective effect partly by favourably increasing the anti-atherogenic high density lipoproteins (HDL)^{18,19}. A causal association is supported by evidence that, after 21 days' abstinence, the pattern reverts to that in non-drinkers²⁰. This is not, however, the only factor, since the changes in HDL can account for only about half the

observed protective effect²¹. There is also evidence that chronic alcohol consumption suppresses levels of the atherogenic lipoprotein(a), which has been shown to rise substantially when alcoholics stop drinking²². In contrast, binge drinkers do not have high HDL levels²³ but instead have high concentrations of the atherogenic low-density lipoproteins (LDL)²⁴. In this context, a key finding comes from a study of 526 patients undergoing coronary arteriography: at each level of alcohol consumption, those drinking variable amounts of alcohol had more coronary occlusion than those drinking regularly²³. Interpretation of these findings has, however, been complicated by uncertainty about recall of drinking levels in this population and the difficulty of separating out the effects of malnutrition and liver dysfunction.

The difficulties of conducting research in man led to a search for an appropriate animal model. Hojnacki *et al.* have shown that the squirrel monkey offers such an opportunity. In a study of alcohol naive monkeys that had been established on a liquid primate diet, they examined whether the effect on lipoprotein levels differed when the same total amount of alcohol was consumed regularly or when it was taken in binges²⁵. After establishing that the monkeys were homogeneous in terms of body weight, liver function, and lipoprotein levels, they assigned them at random to controls, regular drinking, and binge drinking. The controls were maintained on a balanced liquid diet. Regular drinkers received an identical diet except that alcohol was substituted for 12% of the carbohydrate-derived calories. Binge drinkers received the same amount of alcohol administered as 6% of calories for a four-day period followed by 20% of calories for three days. After six months, compared with controls, regular drinkers had raised HDL levels with further cardioprotective changes in subfractions (increased HDL₂/HDL₃ ratio), although LDL levels were similar in regular drinkers and controls. Despite consuming the same overall quantity of alcohol, binge drinkers had a strikingly different profile. HDL levels did not show the cardioprotective pattern seen in regular drinkers and did not differ significantly from controls. Binge drinking was, however associated with significant increases in both LDL and apolipoprotein B, both normally associated with atheroma. The study also examined rates of cholesterol metabolism and, specifically, lecithin:cholesterol acyltransferase (LCAT). LCAT activity was increased in regular drinkers but depressed in binge drinkers to a level seen previously in monkeys receiving 24% of total calories from alcohol.

This study was conducted in circumstances that were more tightly controlled than is possible with human beings, and the results are consistent with the limited evidence from man. Taskinen *et al.* found no alteration in HDL profile in men given 5.5 g/kg bodyweight of ethanol over a

2.5 day period²⁶ and Pikaar found no changes in HDL profile in non-alcoholic men drinking in weekend binges over a five-week period²⁷. One study has revealed higher levels of HDL in those drinking intermittently than in non-drinkers but the consumption of the intermittent drinkers was not high (111 g/week)²⁸. In addition, binge drinking by healthy men can lead to a sustained increase in LDL triglyceride levels in under three days²⁶.

In summary, evidence in man, both real-life and experimental, and in animals, indicates that while regular drinking produces a cardioprotective lipid profile, the same amount of alcohol consumed in binges produces a profile associated with an increased risk of heart disease.

Clotting

The role of the clotting system has come under scrutiny because of both the greater risk of sudden cardiac death in heavy drinkers, which could be due to myocardial infarction caused by thrombosis, and the greater risk of haemorrhagic²⁹ and ischaemic³⁰ stroke. *In-vitro*³¹ and *in-vivo*³² investigations have shown that alcohol inhibits platelet responses to a range of physiological factors and several epidemiological studies have reported reduced platelet aggregation in drinkers^{33,34}. While platelet counts are often low in alcoholics, a study in patients with ischaemic stroke has produced contradictory results, with heavy drinkers more likely than other patients to show both thrombocytosis and thrombocytopenia³⁵.

There is considerable evidence that moderate regular drinking with meals produces effects that are cardioprotective. In a study of the effect of alcohol on fibrinolytic activity, eight men were given 40 g alcohol with their evening meal on four of eleven study days, with mineral water on the remaining days³⁶. The timing was kept constant to allow for the known circadian rhythm in clotting activity. Compared with days when mineral water was taken, alcohol was associated with a rise in tissue-type plasminogen activator antigen and plasminogen activator inhibitor activity. By the morning, the antigen remained raised but the inhibitor had fallen back to normal. This pattern is consistent with a cardioprotective effect which would be most marked in the mornings, when heart attacks are especially common. These findings are, however, of limited generalizability for two reasons. First, the level of consumption was low. Second, since plasminogen activator is produced by the endothelium, the same response may not be seen in patients with extensive atheroma.

The response by the clotting system to alcohol does not seem to be affected by the pattern of drinking, at least in wine drinkers. By use of a latin square design, subjects were allocated over four five-week periods to abstinence, two glasses of red wine per day, four glasses per day, or a

'binge' pattern (none on Monday to Thursday, four glasses on Friday and five each on Saturday and Sunday)²⁷. Platelet aggregation was significantly less after alcohol drinking, four glasses being associated with significantly slower aggregation than abstinence or two glasses. Platelet aggregation, plasminogen, and tissue-type plasminogen activator were not significantly different in binge drinkers and those drinking two glasses per day. There are, however, two reasons why this study may be misleading. First, the samples were analysed during a time when subjects had recently been drinking but adverse changes in the clotting profile may only appear on withdrawal. In a study of alcoholics admitted for detoxification³⁷, subjects had thromboxane levels that were comparable with those of healthy controls who had not drunk alcohol recently. When alcohol was withdrawn they showed a significant increase in production of thromboxane and in platelet aggregation response to ADP, and a shortening in bleeding time. This would be consistent with the notion that cessation, or possibly reduction, of drinking after a binge leads to a rebound increase in propensity to clot. Second, any rebound increase in propensity to clotting could be influenced by the beverage consumed.

In summary, although the evidence is still incomplete, it is consistent with a reduction of thrombosis risk by moderate regular alcohol consumption and an increase by binge drinking or withdrawal after heavy drinking. In addition, regular moderate consumption of red wine may offer some protection from a rebound increase in risk of thrombosis.

Arrhythmias

Reports from several countries of an association between alcohol consumption and sudden cardiac death (the 'holiday heart' syndrome) have led to a series of studies to elucidate the mechanisms. Greenspon and Schaal showed that, in patients with a history of palpitations or light-headedness and moderate or heavy alcohol use, administration of alcohol to achieve blood levels of 0.3–1 g/L was associated with delay in His-ventricular conduction and a range of atrial and ventricular tachyarrhythmias³⁸. Studies of acute administration of alcohol in subjects without a history of chronic alcohol use have, however, not shown any delay in conduction³⁹.

These findings suggest that a combination of chronic and acute alcohol ingestion may be necessary to induce arrhythmias but raises questions about what mechanisms are involved.

The susceptibility of the myocardium to circulating β -agonists has been examined in a study in which dogs were fed for a year on a diet that had 36% of calories as alcohol⁴⁰. Compared with controls, the electrical threshold for

ventricular fibrillation was significantly lower and, unlike in controls, was lowered further by acute administration of alcohol sufficient to produce blood concentrations of 2.13 g/L. Subsequent administration of adrenaline did reduce the threshold in controls but not in alcohol-treated dogs. A possible explanation is that when circulating levels of alcohol are high there is already substantial occupation of β -receptors, limiting the scope for any further effect. If this occupation is reversed by alcohol withdrawal, superimposed on the lowered ventricular fibrillation threshold due to chronic alcohol consumption, it could lead to an enhanced response to catecholamines.

The effects of withdrawal have been examined in a study comparing the responses to isoproterenol, a potent β -agonist, in rats susceptible to isoproterenol-induced ventricular fibrillation. After seven weeks' ingestion of alcohol, half of the rats had alcohol withdrawn the evening before isoproterenol while the others continued to take alcohol. There was also a control group that had not been exposed to alcohol. Arrhythmias were significantly more frequent in the withdrawal group (92% versus 36% in the group that continued to drink) as were the percentage that were fatal (54% versus 9%).

These studies offer a mechanism to explain the observation that, in chronic alcoholics, acute alcohol ingestion⁴¹ and withdrawal are both associated with arrhythmias.

The preceding studies have focused on the cardiac response to circulating catecholamines during alcohol consumption but have not addressed the question of whether alcohol causes permanent damage to the heart. Alcoholic cardiomyopathy is a well recognized condition but studies in man have been complicated by the presence of nutritional and electrolyte disturbances, raising the possibility that it may be due to coexistent micronutrient deficiencies. This interpretation is contradicted by a study of long-term oral administration of alcohol in dogs, showing that damage to the ventricular conduction system and myocardium occurred in the absence of nutritional and electrolyte disturbances⁴². This effect could, however, be mediated by acetaldehyde⁴³, the major metabolite of alcohol, the level of which is influenced by various factors. This hypothesis has been examined by direct infusion of alcohol into the left circumflex arteries of dogs to achieve coronary sinus concentrations of 0.44–2 g/L⁴⁴. Electrophysiological studies were performed 48 hours after cessation of the infusion. 5 of 22 dogs showed evidence of irreversible myocardial injury within the distribution of the left circumflex artery. Provocative ventricular pacing produced arrhythmias in 14 dogs, typically ventricular tachycardia of greater than 240 beats/minute. The arrhythmias had characteristics of re-entry phenomena. Histology showed a range of changes from necrotizing

lesions to areas of fibrous scarring although some changes, albeit much fewer, were also present in controls that had had intra-coronary saline infusions. The lesions were similar to those previously recorded in human beings with a history of heavy drinking and sudden death¹⁷.

In summary, chronic alcohol consumption, even in the absence of nutritional deficiency, seems capable of predisposing the heart to arrhythmias induced by acute alcohol ingestion, both by reducing the threshold for ventricular fibrillation and by causing scarring of the myocardium. In addition, the myocardium may be especially sensitive to catecholamines during withdrawal, as will occur with weekend binges.

Hypertension

Alcohol has an acute pressor effect⁴⁵ but also appears to be an important cause of chronic hypertension, with one study suggesting that it can account for 10% of cases of hypertension in middle-aged British men⁴⁶. The INTER-SALT study, which obtained data on the relationship between blood pressure and alcohol consumption in 48 locations world-wide, revealed a significant association between heavy drinking and hypertension⁴⁷ but the authors noted that the pattern of drinking as well as the quantity seemed important, the greatest difference being between teetotallers and drinkers whose consumption varied, although they did not look specifically at binge drinking. One study has done so, in Finland, where heavy weekend drinkers were found to have significantly higher systolic but not diastolic blood pressures than teetotallers but both systolic and diastolic pressures were higher in heavy daily drinkers⁴⁸. The authors concluded that if weekend binge drinking had any effect on diastolic pressure it was rapidly reversible, although it did appear to have a sustained effect on systolic pressure.

CONCLUSION

On its own, the evidence presented here cannot prove that the pattern of drinking is responsible for the apparent link between alcohol consumption and heart disease. This will require long-term cohort studies that include data on both amount consumed and pattern of drinking. Unfortunately, most studies in progress include only the former. The scale of the problem of premature death in Russia is such, however, that action is needed now. As noted earlier, a major objection to addressing the issue of alcohol has been that research in the west has consistently shown a cardioprotective effect so there is no basis for attributing to it the changing rates of cardiovascular death seen in Russia.

The importance of the research reviewed here is that it shows that we cannot safely extrapolate data from western

countries characterized predominantly by moderate regular drinking to a culture such as that in Russia where there is widespread binge drinking. As noted above, the Russian phenomenon is not unique. One reason for the dearth of research on problem and binge drinkers is that their identification and follow-up is exceptionally difficult. This also poses a difficulty for those undertaking research on patients with myocardial infarctions if they are recruited from hospitals, since such individuals are more likely to die suddenly. Hence, such research should differentiate sudden cardiac death from non-fatal myocardial infarction. This was done in a study undertaken in England in the 1970s, which found that individuals who died suddenly drank more, and were more likely to have taken alcohol in the preceding three hours, than matched patients with non-fatal myocardial infarctions⁴⁹. Interestingly, as in Moscow, there was a weekend peak in sudden cardiac deaths.

The research on lipids shows that binge drinking does not produce the increase in HDL seen with moderate consumption and also has an adverse effect on LDL. This could explain the apparent absence of cardioprotective effect in Russians¹⁰ but, as the relevant study did not measure pattern of drinking, this must remain speculative. While regular moderate alcohol consumption reduces the risk of thrombosis, withdrawal or the period after a binge is marked by an increased risk of thrombosis. Other components of wine may offer some protection from this rebound but protection is not seen with spirits. Chronic alcohol consumption has also been shown to damage the heart and, specifically, the ventricular conduction system. Furthermore, circulating alcohol has a direct effect on the threshold for ventricular fibrillation and during withdrawal the myocardium is rendered more sensitive to catecholamines. This is at a time when platelet aggregation is increased and thus the risk of ischaemia, which will trigger release of catecholamines, will be greatest. Any effects mediated through changes in blood pressure seem limited, although the acute pressor effect could contribute to the observed increase in cerebrovascular disease in heavy drinkers⁵⁰.

This review has indicated that the known effects of binge drinking are different from those seen with regular, moderate drinking and, specifically, are consistent with the apparent association between alcohol consumption and cardiovascular disease and, especially, sudden cardiac death seen in eastern Europe. It has, however, wider implications. For many years Ledermann's theory on the distribution of drinking within a population was widely accepted. In brief, this stated that, within a population, knowledge of the mean level of alcohol consumption was sufficient to describe the distribution of those drinking at different levels⁵¹. This is now known to be incorrect⁵² so those seeking to assess the harm arising from alcohol in a particular society must

determine the actual distribution of levels of drinking. The evidence reviewed here emphasizes the additional importance of determining the pattern of drinking. A recent study of the epidemiology of cirrhosis, which showed the importance of episodic drinking other than with meals, also indicates that the pattern of drinking may be important for other aspects of alcohol-related damage to health⁵³.

These observations have important implications for policy makers, especially those seeking to promote 'sensible drinking'. It is essential that they present clearly the message that, while regular moderate drinking may be good for your heart, the same amount drunk irregularly, in binges, may have the opposite effect. Any public campaign also needs to recognize that binge drinkers are often on the margins of society⁵⁴, and that in some settings they include a rising proportion of women⁵⁵.

Acknowledgement This work was funded by the UK Department for International Development (DfID). However DfID can accept no responsibility for any information provided or views expressed.

REFERENCES

- 1 Leon D, Chenet L, Shkolnikov VM, *et al.* Huge variation in Russian mortality rates 1984–1994: artefact, alcohol, or what? *Lancet* 1997;**350**:383–8
- 2 Walberg P, McKee M, Shkolnikov V, Chenet L, Leon DA. Economic change, crime, and the Russian mortality crisis: a regional analysis. *BMJ* (in press)
- 3 Murray CJL, Lopez AD, eds. *The Global Burden of Disease*. Boston: WHO, Harvard School of Public Health, World Bank, 1996:307–8
- 4 Simpura J. Trends in alcohol consumption and drinking patterns: lessons from world-wide development. In: Holder HD, Edwards G, eds. *Alcohol Policy and Public Policy: Evidence and Issues*. Oxford: Oxford Medical Publications, 1995:9–37
- 5 Ryan M. Alcoholism and rising mortality in the Russian Federation. *BMJ* 1995;**310**:646–8
- 6 White S. *Russia Goes Dry*. Cambridge: Cambridge University Press, 1996
- 7 Anderson P, Cremona A, Paton A, Turner C, Wallace P. The risk of alcohol. *Addiction* 1993;**88**:1493–508
- 8 Poikolainen K. Alcohol and mortality: a review. *J Clin Epidemiol* 1995;**48**:455–65
- 9 Holman CDJ, English DR, Milne E, Winter MG. Meta-analysis of alcohol and all-cause mortality: a validation of NHMRC recommendations. *Med J Austr* 1996;**164**:141–5
- 10 Deev A, Shestov D, Abernathy J, Kapustina A, Mahina N, Irving S. Association of alcohol consumption to mortality in middle-aged US and Russian men and women. *Ann Epidemiol* 1998;**8**:147–53
- 11 Rossnow I, Amundsen A. Alcohol abuse and mortality: a 40-year prospective study of Norwegian conscripts. *Soc Sci Med* 1997;**44**:261–7
- 12 Rosengren A, Wilhelmsen L, Pennert K, Berglund G, Elmfeldt D. Alcoholic intemperance, coronary heart disease and mortality in middle-aged Swedish men. *Acta Med Scand* 1987;**222**:201–13
- 13 Dyer AR, Stamler J, Paul O, *et al.* Alcohol consumption, cardiovascular risk factors, and mortality in two Chicago epidemiologic studies. *Circulation* 1997;**56**:1067–74

- 14 Kauhanen J, Kaplan GA, Goldberg DD, Cohen RD, Lakka TA, Salonen JT. Frequent hangovers and cardiovascular mortality in middle-aged men. *Epidemiology* 1997;8:310-14
- 15 Kauhanen J, Kaplan GA, Goldberg DE, Salonen JT. Beer bingeing and mortality: results from the Kuopio ischaemic heart disease risk factor study, a prospective population based study. *BMJ* 1997;315:846-51
- 16 Chenet L, McKee M, Leon D, Shkolnikov V, Vassin S. Alcohol and cardiovascular mortality in Moscow, new evidence of a causal association. *J Epidemiol Comm Health* (in press)
- 17 Vikhert AM, Tsiplenkova VG, Cherpachenko NM. Alcoholic cardiomyopathy and sudden cardiac death. *JACC* 1986;8:3A-11A
- 18 Criqui MH. Alcohol consumption, blood pressure, lipids and cardiovascular mortality. *Alcohol Clin Exp Res* 1986;10:564-9
- 19 Frohlich JJ. Effects of alcohol on plasma lipoprotein metabolism. *Clin Chim Acta* 1996;246:39-49
- 20 Lecomte E, Herbeth B, Paille F, Steinmetz J, Artur Y, Siest G. Changes in serum apolipoprotein and lipoprotein profile induced by chronic alcohol consumption and withdrawal: determinant effect on heart disease? *Clin Chem* 1996;42:1666-75
- 21 Suh I, Shaten BJ, Cutler JA, et al. Alcohol use and mortality from coronary heart disease: the role of high density lipoprotein cholesterol. *Ann Intern Med* 1992;116:881-7
- 22 Kervinen K, Savolainen MJ, Kesaniemi YA. A rapid increase in lipoprotein (a) levels after ethanol withdrawal in alcoholic men. *Life Sci* 1991;48:2183-8
- 23 Gruchow HW, Hoffmann RG, Anderson AJ, Barboriak JJ. Effects of drinking patterns on the relationship between alcohol and coronary occlusion. *Atherosclerosis* 1982;43:393-404
- 24 Gruchow HW, Sobocinski KA, Barboriak JJ, Anderson AJ. Apolipoproteins and alcohol intake patterns. *CVD Epidemiol Newsletter* 1987;41:24
- 25 Hojnacki JL, Deschenes RN, Cuette-Brown JE, Mulligan JJ, Osmolski TV, Renicca NJ, Barboriak JL. Effect of drinking pattern on plasma lipoproteins and body weight. *Atherosclerosis* 1991;88:49-59
- 26 Taskinen MR, Valimaki M, Nikkila EA, Kuusi T, Ylikahri R. Sequence of alcohol-induced initial changes in plasma lipoproteins (VLDL and HDL) and lipolytic enzymes in humans. *Metabolism* 1985;34:112-19
- 27 Pikaar NA, Wedel M, Van der Beek EJ, et al. Effects of moderate alcohol consumption on platelet aggregation, fibrinolysis, and blood lipids. *Metabolism* 1987;36:538-43
- 28 Frimpong NA, Lapp JA. Effects of moderate alcohol intake in fixed or variable amounts on concentration of serum lipids and liver enzymes in healthy young men. *Am J Clin Nutr* 1989;50:987-91
- 29 Stampfer MJ, Colditz GA, Willett WC, Spiezer FE, Hennekens CH. A prospective study of moderate alcohol consumption and the risk of coronary heart disease and stroke in women. *N Engl J Med* 1988;319:267-73
- 30 Hillbom ME, Kaste M. Alcohol intoxication: A risk factor for ischaemic brain infarction. *Stroke* 1983;14:693-9
- 31 Rubin R, Rand ML. Alcohol and platelet function. *Alcohol Clin Exp Res* 1994;18:105-10
- 32 Dong QS, Karanian JW, Wesely L, Myers AK. Inhibition of platelet aggregation in whole blood after exposure of rats to alcohol by inhalation. *Alcohol* 1997;14:49-54
- 33 Renaud S, McGregor L, Martin JL. Influence of alcohol on platelet functions in relation to atherosclerosis. In Pozza G, Micossi P, Catapano AL, eds. *Diet, Diabetes and Atherosclerosis*. New York: Raven, 1984:177-87
- 34 Meade TW, Vickers MV, Thompson SG, et al. Epidemiological characteristics of platelet aggregability *BMJ* 1985;290:428-32
- 35 Numminen H, Hillbom M, Juvela S. Platelets, alcohol consumption, and onset of brain infarction. *J Neurol Neurosurg Psychiatry* 1996;61:376-80
- 36 Hendriks HFJ, Veenstra J, Velthuis-te Wierik EJM, Schaafsma G, Kluft C. Effect of moderate dose of alcohol with evening meal on fibrinolytic factors. *BMJ* 1994;308:1003-6
- 37 Hillbom M, Kangasaho M, Löwbeer C, Kaste M, Muuronen A, Numminen H. Effects of alcohol on platelet function. *Alcohol* 1985;2:429-32
- 38 Greenspon AJ, Schaal SF. The 'holiday heart': electrophysiological studies of alcohol effects in alcoholics. *Ann Intern Med* 1983;98:135-9
- 39 Gould L, Reddy CVR, Becker W, Oh K, Kim SG. Electrophysiologic properties of alcohol in man. *J Electrocardiogr* 1978;11:219-26
- 40 Patel R, McArdle JJ, Regan TJ. Increased ventricular vulnerability in a chronic ethanol model despite reduced electrophysiologic responses to catecholamines. *Alc Clin Exp Res* 1991;15:785-9
- 41 Greenspon AJ, Stang JM, Lewis RP, Schaal SF. Provocation of ventricular tachycardia after consumption of alcohol. *N Engl J Med* 1979;301:1049-50
- 42 Ettinger PO, Lyons M, Oldewurtel HA, Regan TJ. Cardiac conduction abnormalities produced by chronic alcoholism. *Am Heart J* 1976;91:66-78
- 43 Schreiber SS, Oratz M, Rothschild MA, Reff F, Evans C. Alcoholic cardiomyopathy. II. The inhibition of cardiac microsomal protein synthesis by acetaldehyde. *J Mol Cell Cardiol* 1974;6:207-15
- 44 Patterson E, Dormer KJ, Scherlag BJ, Kosanke SD, Schaper J, Lazzara R. Long-term intracoronary ethanol administration electrophysiological and morphological effects. *Alcohol* 1987;4:375-84
- 45 Potter JF, Watson RDS, Skan W, Beevers DG. The pressor and metabolic effects of alcohol in normotensives. *Hypertension* 1986;8:625-31
- 46 Shaper AG, Wannamethee G, Whincup P. Alcohol and blood pressure in middle-aged British men. *J Hum Hypertens* 1988;2:71-8
- 47 Marmot MG, Elliott P, Shipley MJ, et al. Alcohol and blood pressure: the INTERSALT study. *BMJ* 1994;308:1263-7
- 48 Seppä K, Laippala P, Sillanaukee P. Drinking pattern and blood pressure. *Am J Hypertens* 1994;7:249-54
- 49 Myers A, Dewar HA. Circumstances attending 100 sudden deaths from coronary artery disease with coroner's necropsies. *Br Heart J* 1975;37:1133-43
- 50 Anderson P. Alcohol and the risk of physical harm. In: Holder HD, Edwards G, eds. *Alcohol Policy and Public Policy: Evidence and Issues*. Oxford: Oxford Medical Publications, 1995:38-61
- 51 Ledermann S. *Alcool, alcoolisme, alcoolisation*, vol 1. Paris: Presses Universitaires de France, 1956
- 52 Skog O-J. The collectivity of drinking culture: a theory of the distribution of alcohol consumption. *Br J Addiction* 1985;80:83-99
- 53 Bellentani S, Saccoccio G, Costa G, et al. Drinking habits as cofactors of risk for alcohol induced liver damage. *Gut* 1997;41:845-50
- 54 Lee AJ, Crombie IK, Smith WCS, Tunstall-Pedoe H. Alcohol consumption and unemployment among men: the Scottish Heart Health Study. *Br J Addiction* 1990;85:1165-70
- 55 Mercer PW, Khavari K. Are women drinking more like men? An empirical examination of the convergence hypothesis. *Alc Clin Exp Res* 1990;14:461-6