Average volume of alcohol consumption, patterns of drinking and risk of coronary heart disease – a review

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The effect of average volume of alcohol on coronary heart disease (CHD) is J-shaped in established market economies. Light to moderate drinkers have less risk than abstainers, with heavy drinkers displaying the highest level of risk. This relationship between average volume of alcohol consumption and CHD is modified by different patterns of drinking. Heavy drinking occasions as well as drinking outside meals are related to increased CHD risk, independently of volume of drinking. Beverage type does not seem to have much impact, even though there are some indications that wine is more protective than other forms of alcohol. Physiological mechanisms have been identified to explain this complex relationship between alcohol and CHD. Since patterns of drinking are important in determining CHD risk, they should be included in future epidemiologic studies, together with biomarkers further to test hypotheses about pathways. *J Cardiovasc Risk* 10:15–20 © 2003 Lippincott Williams & Wilkins.

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Introduction

Patterns of drinking have recently come to the attention of epidemiology research [1], and this interest in patterns has been increased by the discussion about the role of alcohol in the fluctuations of mortality in Russia in the past 20 years [2–7]. Recently, there have been two reviews on this topic: Puddey and colleagues [8] reviewed the influence of patterns of drinking on cardiovascular disease and risk factors, and McKee and Britton [9] reviewed physiological mechanisms which may be responsible for the detrimental effects of heavy drinking occasions on cardiovascular disease (CVD). This review focuses on contributions appearing after the above-mentioned reviews.

Average volume of alcohol consumption and CHD

Average volume of drinking and CHD seems to show a J-shape relationship in customary medical epidemiological cohort studies in established market economies [10]. Compared with abstinence from alcohol, low to moderate average consumption of alcohol has been found to be associated with lower risk for CHD incidence and mortality. For higher levels of average volume of alcohol consumption, the risk relationship reverses [10,11], with heavy average consumption being associated with risks larger than the risks for abstainers. Corrao and colleagues [10] in the most recent meta-analysis demonstrated the described J-shape, and in addition demonstrated several other characteristics of the literature on average volume of consumption and CHD:

1. There was a pronounced gender effect showing women had less protective effects at the same level of consumption, and an earlier upturn of the curve.
2. For fatal outcomes the beneficial effect of alcohol was less pronounced than for non-fatal outcomes.
3. There was heterogeneity in the studies especially with respect to RRs for higher intake, indicating additional influencing factors not controlled for.
4. Better quality studies had the maximal beneficial effect at lower levels of average alcohol intake (maximum protective effect at 20 g average pure alcohol intake per day; the RR = 1 line equivalent to abstainers' risk was crossed at 72 g average intake, and there was a significant detrimental effect after 89 g average intake per day).
5. Specifically, wholly adjusted studies, studies comparing against lifetime abstainers, studies excluding sick subjects at baseline and cohort studies showed less beneficial effects in comparisons to unadjusted or partially adjusted studies, compared with current abstainers, inclusions of sick subjects and case–control studies.

The epidemiological evidence that light to moderate average alcohol consumption protects against CHD is strengthened by growing and, in some instances, substantial evidence concerning the biological mechanisms by which a protective effect could be mediated [12–17]. First, moderate alcohol intake has been clearly linked to favourable lipid profiles, especially an increase in high density lipoproteins (HDL) [16,18]. It has been

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estimated that as much as 40–50% of the protective effect may be attributable to this mechanism [19,20]. Secondly, moderate alcohol intake favourably affects coagulation profiles [16], in particular, through its effects on platelet aggregation [21] and fibrinolysis [22]. A recent meta-analysis on 42 published trials confirmed both pathways, the influence of alcohol on lipids and on blood-clotting factors [16].

Thirdly, low to moderate consumption of alcohol has been shown favourably to affect insulin resistance [13,23,24]. Fourthly, it has been postulated that alcohol could protect against IHD through its effect on hormonal profiles, in particular, its oestrogenic effects [14]. Fifthly, the alcohol metabolite acetate has been postulated to protect against CHD by promoting vasodilatation [25]. Sixthly, alcohol may also affect the inflammation associated with atherosclerotic plaques and by this pathway may influence CHD [26–28]. Overall, the physiological pathways 3–6 are much less experimentally supported than the effects of light to moderate consumption on lipids and blood-clotting factors.

The protective effect of light to moderate consumption has been criticized for several reasons. Since 1988 the question of a comparison group has been raised [29–31], first in the form of the sick-quitter hypothesis, that is, that in the abstainer group, there are people who quit drinking because of health reasons and this may be responsible for the elevated disease risk compared with light and moderate drinkers. However, many subsequent papers controlled for this effect by taking lifetime abstainers as the comparison group [32]. Still, in most established market economies, where most of the research on alcohol and CHD took place, abstainers constitute only a minority within the general population, and it cannot be excluded that they have other behavioural characteristics responsible for the elevated CHD risk. While such a possibility can never be excluded, no alternative explanation has ever been empirically demonstrated. For instance, social isolation has been theoretically claimed to confound the alcohol–mortality relationship [33], but empirical research could not substantiate this effect [34].

In sum, the relationship between average volume of drinking and CHD seems to be J-shaped. Light to moderate drinking is associated with a lower CHD risk than abstaining or heavy drinking. However, the studies on average volume of consumption and CHD are heterogeneous, indicating that factors other than those included in the study co-determine the relationship. One of the main factors determining the relationship between average volume and CHD risk may be the pattern of drinking, that is, the way in which the same average amount of alcohol is consumed.

Patterns of drinking and CHD

Heavy drinking occasions

Heavy drinking occasions have been linked to adverse cardiovascular events for some time [35]. However, many studies had used wider endpoints than CHD [36], or used samples of problem drinkers or persons with alcohol use disorders [37–39], where heavy drinking patterns are confounded with volume.

However, some of the more recent studies controlled for (average) volume of drinking. In a case–control study in Australia [40] a comparison was made between 11 511 cases of acute myocardial infarction or coronary death with 6077 randomly selected population controls. If people drank in binges (usually women had five or more drinks on an occasion, men had nine or more drinks on an occasion), there were no protective effects for coronary events and mainly relative risks larger than one compared with abstainers, that is, indicating higher risks for major coronary events. This elevated risk was even present in groups with low overall volume of drinking. As expected, the authors also found a protective effect for daily drinkers, which was most pronounced for regular, light to moderate drinkers.

Similarly, Murray and colleagues [41] evaluated cardiovascular consequences of binge drinking (eight or more drinks at a sitting) and usual (nonbinge) drinking of alcohol in a longitudinal, population-based study. Interview data from 1154 men and women aged 18 to 65 in Winnipeg, Manitoba, Canada were linked to health care utilization and mortality records. Using an 8-year follow-up period, Cox proportional hazards regressions were separately performed for men and women, on time to first event for physician visits, hospitalizations and deaths due to CHD, hypertension, or other cardiovascular disease (CVD). Binge drinking increased the risk of CHD in men (Hazard Ratio (HR) = 2.3; 95% CI = 1.2–4.2) and women (HR = 1.1; 95% CI = 1.02–1.2) and increased the risk of hypertension in men (HR = 1.6; 95% CI = 1.04–2.4) but not women. Binge drinking had no effect on the risk of other CVD. All of these results were controlled for average volume of drinking. Again, the expected cardioprotective effects were confirmed in both men and women. The harmful effects of heavy drinking occasions on CHD morbidity and mortality could thus be disaggregated from the effect of average volume of drinking.

Trevisan and colleagues [42] found in a case–control design that after adjustment for average volume of consumption, weekend drinking in men was significantly related to risk of myocardial infarction compared with men who drank less than once a week (logistic regression: Odds Ratio 1.7; 95% CI = 1.1–2.8).

In addition to the effect on CHD, there appears to be a relationship between irregular heavy drinking occasions

and other forms of cardiovascular death, especially sudden cardiac death [36,43,44]. This is consistent with the physiological mechanisms of increased clotting and reducing the threshold for ventricular fibrillation after heavy drinking occasions, which have been reviewed by McKee and Britton [9]: Specifically, heavy drinking occasion have been shown to increase low-density lipoproteins, which in turn have been linked to negative cardiovascular outcomes. Contrary to low or moderate steady drinking, heavy irregular drinking occasions are not associated with an increase of high-density lipoproteins, which themselves have been linked to favourable cardiovascular outcomes. In addition, irregular drinking is associated with increased risk of thrombosis, occurring after cessation of drinking [45]. Finally, irregular heavy drinking seems to predispose to histological changes in the myocardium and conducting system, as well as to a reduction in the threshold for ventricular fibrillation. In sum, irregular heavy drinking occasions are mainly associated with physiological mechanisms increasing the risk of sudden cardiac death and other cardiovascular outcomes, in contrast to the physiological mechanisms triggered by steady low to moderate consumption and linked to favourable cardiac outcomes. However, individual level studies are still scarce and there are studies showing no effects [46].

Given the described scarcity of individual level studies, it is not surprising that much of the discussion on patterns of drinking and outcomes is based on aggregate level studies, especially on the Russian experiences with the natural experiment of the Gorbachev anti-alcohol campaign. Russia is generally considered one of the countries with the highest rate of irregular heavy drinking occasions [47,48]. Thus, if a drinking style of heavy drinking occasions has an adverse impact on CVD in general and on CHD in particular, such effects should have become evident in the experience of the anti-alcohol campaign of the last years of the Soviet Union. In the period 1984–1987, when estimated total alcohol consumption in Russia fell by about 25% [49], age-adjusted male deaths from circulatory disease fell by 9% [2]. After the end of the campaign, the death rate rose again, quite dramatically. The interpretation of alcohol's role in the recent drastic upward changes in mortality in Russia remains controversial, as there were many other social changes occurring in the late 1980s and early 1990s [2–7]. However, there seems to be agreement that alcohol has played a role in increasing mortality rates, but the level of involvement seems to be still under discussion. It is also not clear to what extent the detrimental effect of alcohol was due to CHD and to what degree to other cardiovascular causes of disease. The main problem was to define a comparable set of ICD codes for Coronary Heart Disease (ICD 9: 410–414). The Soviet Union, and later Russia, used, at that time, a coding system very different from the ICD.

There is another indirect line of research on the effect of heavy drinking occasions on CHD. It has been shown that in countries with a tradition of heavier or binge drinking at the weekend show over-proportionally high CHD mortality on Mondays [50–52].

To sum up the individual level and aggregate level studies: heavy drinking occasions have been linked to increased CHD morbidity and mortality. In addition, heavy drinking occasions have been related to cardiac arrhythmias, sudden cardiac death and other forms of cardiovascular outcomes. As with the protective effect, there are plausible physiological mechanisms, and results from individual and aggregate level studies converge to a certain degree. However, there are still many open questions on mechanisms, the strength of the effect and its generalization to different cardiovascular outcomes.

Drinking with meals

Trevisan and colleagues [53] reported on drinking with meals and CHD mortality based on the Risk Factor and Life Expectancy Study, a pooled series of epidemiological studies conducted in Italy with 8647 males and 6521 females, age 30–59 at baseline and free of cardiovascular disease. Subjects were followed up on average for 7 years. With respect to CHD, alcohol showed a protective effect, and drinking wine with meals was linked to more positive outcomes than drinking wine outside meals. Compared with drinking with meals as a reference category, drinking wine outside meals had a relative risk of 1.8 (95% CI 0.97–3.5) for CHD in males, adjusted for average volume of drinking and other potential confounders. There were not enough CHD cases to conduct a similar analysis for females, but the effects for all-cause mortality for females showed a fivefold risk for wine outside meals compared with wine with meals (RR: 5.0; 95% CI: 1.5–10.9).

In another study of the same principal author and his colleagues [42] using a case–control design, an examination was made of 443 male myocardial infarction survivors and 922 healthy controls 35–69 years old. Findings were that compared with nondrinkers, the age, education and smoking adjusted odds ratios for former drinkers and current drinkers were 0.67 (95% CI: 0.32–1.38) and 0.47 (95% CI: 0.24–0.95) respectively, confirming the overall cardioprotective effect of alcohol consumption (see above). With respect to drinking with meals, men who reported drinking without food at least 75% of the time had an odds ratio of 1.5 (95% confidence interval 1.0–2.3) compared with those who drank mainly with meals and snacks, after adjustment for age, education and volume of alcohol consumed.

The potential mechanisms linking consumption of alcoholic beverages with a meal to a lower CHD risk compared with consumption away from meals is still not clear; however, few have been hypothesized. A study by Trevisan and colleages [54] in a large sample of Italian men and women found a significant association between drinking outside meals and a higher prevalence of hypertension, compared with drinking with meals, even after adjustment for differences in alcohol consumption between these drinking pattern categories. These findings were recently confirmed in another study using a population-based sample in the USA [55]. Finally, Foppa and colleagues [56] found in a controlled randomized trial that moderate consumption of wine with the meal reduced post-prandial blood pressure. Drinking with meals has also been shown positively to affect fibrinolysis [57] and lipids [58].

Potential physiological links between drinking with meals and these CHD risk factors also include a reduced absorption of alcohol due to the presence of food in the gastrointestinal tract [59]. Another physiological link may be that food increases the alcohol elimination rate [60].

Drinking alcohol with or without food may also just represent a certain lifestyle, which may itself be the link to protective and detrimental health effects [61]. For example, in many established market economies, regular meals with wine is one of the characteristics of the middle- and upper-class, and social gradient is strongly related to almost all morbidity and mortality indicators.

Beverage-specific effects

Rimm and colleagues [62] reviewed the literature with respect to beverage-specific effects on CHD and could not find any systematic effects. Although there have been many more publications on this topic since their review, no systematic pattern or results have emerged. Perhaps most notably in this respect are the findings of similar protective effects for Bavaria (Germany) and the Czech Republic [63–64] as for Mediterranean countries. Bavaria and the Czech Republic are regions where beer is consumed in a way similar to the consumption of wine in Mediterranean countries: regularly on an almost daily basis with meals.

The overall problem with beverage effects is, however, that beverage preferences in most cultures are linked with other variables such as socio-economic status and lifestyle variables [61]. These linkages may not be the same for different cultures, but many countries show clear co-variation. This makes it almost impossible to separate effects of beverages from other effects.

In terms of physiological mechanisms, it is possible that some of the protective effect is mediated through the antioxidative constituents of wine [65]. However, as discussed above, most of the protective effect appears to be linked to ethanol, *per se*.

Conclusions

Patterns of drinking alcohol were linked to beneficial and detrimental effects on CHD morbidity and mortality. Unfortunately, this line of research, on the relationship between patterns of drinking and other health outcomes, has just started. In future, epidemiologists need to address the complex issue of alcohol and health with a more sophisticated approach to the characterization of alcohol use. To take the impact of patterns seriously, it will also be necessary to include biomarkers for the various processes outlined above into population-based studies. This will hopefully result in fewer studies of better quality, specifically addressing hypotheses about relationships and physiological pathways in the same study. But the implications of such studies both for prevention and policy will be much clearer.

References

*Of special interest
**Of outstanding interest

1 Rehm J, Ashley MJ, Room R, Single E, Bondy S, Ferrence R, *et al.* Drinking patterns and their consequences: report from an international meeting. *Addiction* 1996; **91**:1615–1621.

2 Leon DA, Chenet L, Shkolnikov V, Zakharov S, Shapiro J, Rakhmanova G, *et al.* Huge variation in Russian mortality rates 1984–94: artefact, alcohol, or what? *Lancet* 1997; **350**:383–388.

*In Russia, all major causes of death, with the exception of neoplasms, showed declines in mortality between 1984 and 1987 and increases between 1987 and 1994. The largest declines and subsequent increases in proportional terms were observed for alcohol-related deaths and accidents and violence. But there were also substantial changes in circulatory disease, which may be attributed to patterns of drinking.

3 Notzon FC, Komarov YM, Ermakov SP, Sempos CT, Marks JS, Sempos EV. Causes of declining life expectancy in Russia. *JAMA* 1998; **279**:793–800.

4 Bobak M, Marmot M. Alcohol and mortality in Russia: is it different than elsewhere? *Ann Epidemiol* 1999; **9**:335–338.

5 Britton A, McKee M. The relation between alcohol and cardiovascular disease in Eastern Europe: explaining the paradox. *J Epidemiol Community Health* 2000; **54**:328–332.

6 McKee M, Shkolnikov V, Leon DA. Alcohol is implicated in the fluctuations in cardiovascular disease in Russia since the 1980s. *Ann Epidemiol* 2001; **11**:1–6.

7 Shkolnikov V, McKee M, Leon DA. Changes in live expectancy in Russia in the mid-1990s. *Lancet* 2001; **357**:917–921.

8 Puddey IB, Rakic V, Dimmitt SB, Beilin LJ. Influence of drinking on cardiovascular disease and cardiovascular risk factors – a review. *Addiction* 1999; **94**:649–663.

**Overview on patterns of drinking and cardiovascular risk, including both epidemiological and physiological studies. Provided good evidence that patterns of drinking were crucial in deciding beneficial vs. detrimental CVD effects in part independent of average volume of consumption.

9 McKee M, Britton A. The positive relationship between alcohol and heart disease in eastern Europe: potential physiological mechanisms. *J Roy Soc Med* 1998; **91**:402–407.

*Overview on physiological mechanism which may explain the consequences of heavy drinking occasions and CHD.

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

*Meta analysis on average volume of alcohol consumption and CHD. Main result was a J-shape, although there was heterogeneity between studies. Also identified potential influencing factors on this relationship.

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

12 Renaud SC, Criqui MH, Farchi G, Veenstra J. Alcohol drinking and coronary heart disease. In: Verschuren PM, editor. *Health issues related to alcohol consumption.* Washington, DC: International Life Sciences Institute; 1993. pp. 81–123.
13 Rankin J. Biological mechanisms at moderate levels of alcohol consumption that may affect coronary heart disease. *Contemporary Drug Problems* 1994; **21**:45–57.
14 Svärdsudd K. Moderate alcohol consumption and cardiovascular disease: is there evidence for a preventive effect? *Alcohol Clin Exp Res* 1998; **22**:307S–314S.
15 Single E, Ashley MJ, Bondy S, Rankin J, Rehm J. Evidence regarding the level of alcohol consumption considered to be low-risk for men and women. Final report submitted to the Australian Commonwealth Department of Health and Aged Care, 1999.
16 Rimm EB, Williams, P, Fosher K, Criqui M, Stampfer MJ. Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors. *BMJ* 1999; **319**:1523–1528.
*Meta analysis on studies with short time effects of alcohol on CHD risk factors. Confirmed beneficial effects on lipid profiles and blood clotting factors.
17 Mukamal KJ, Rimm EB. Alcohol's effects on the risk for coronary heart disease. *Alcohol Res Health* 2001; **25**:255–261.
18 Baraona E, Lieber CS. Alcohol and lipids. In: Galanter M, editor. *The consequences of alcoholism.* New York: Plenum Press; 1998. pp. 97–134.
19 Criqui MH, Cowan LD, Tyroler JA, Bangdiwala S, Heiss G, Wallace RB, *et al.* Lipoprotein medicators for the effects of alcohol consumption and cigarette smoking on cardiovascular mortality. Results from the Lipid Research Clinics Follow-up Study. *Am J Epidemiol* 1987; **126**:629–637.
20 Criqui MH, Ringel BL. Does diet or alcohol explain the French paradox? *Lancet* 1994; **344**:1719–1723.
21 McKenzie CR, Eisenberg PR. Alcohol, coagulation, and arterial thrombosis. In: Zakhari S, Wassef M, editors. *Alcohol and the cardiovascular system.* Bethesda, MD: National Institues of Health, National Institute on Alcohol Abuse and Alcoholism; 1996. pp. 413–439.
22 Reeder VC, Aikens ML, Li X-N, Booyse FM. Alcohol and the fibrinolytic system. In: Zakhari S, Wassef M, editors. *Alcohol and the cardiovascular system.* Bethesda, MD: National Institutes of Health, National Institute on Alcohol Abuse and Alcoholism; 1996. pp. 391–411.
23 Kiechl S, Willeit J, Poewe W, Egger G, Oberhollenzer F, Muggeo M, Bonora E. Insulin sensitivity and regular alcohol consumption: large, prospective, cross sectional population study (Bruneck study). *BMJ* 1996; **313**: 1040–1044.
24 Lazarus R, Sparrow D, Weiss ST. Alcohol intake and insulin levels. The Normative Aging Study. *Am J Epidemiol* 1997; **145**:909–916.
25 US Department of Health and Human Services. Ninth Special Report to the US Congress on Alcohol, and Health, Vol. No. 97-4017. Rockville, MD: US Department of Health and Human Services, National Institute on Alcohol Abuse and Alcoholism (NIAAA); 1997.
26 Imhof A, Froehlich M, Brenner H, Boeing H, Pepys MB, Koenig W. Effect of alcohol consumption on systemic markers of inflammation. *Lancet* 2001; **357**:763–767.
27 Ridker PM. Role of inflammatory biomarkers in prediction of coronary heart disease. *Lancet* 2001; **358**:946–948.
28 Morrow DA, Ridker PM. C-reactive protein, inflammation, and coronary risk. *Med Clin N Am* 2000; **84**:149–161.
29 Shaper AG, Wannamethee G, Walker M. Alcohol and mortality in British men: explaining the U-shaped curve. *Lancet* 1988; **ii**:1267–1273.
*Classic on sick quitter effect: Points out the importance of comparing against lifetime abstainers.
30 Shaper AG. Alcohol and mortality: a review of prospective studies. *Br J Addiction* 1990; **85**:837–847.
31 Shaper AG. A response to commentaries: the effects of self-selection. *Br J Addiction* 1990; **85**:859–861.
32 Rehm J, Sempos CT. Alcohol consumption and mortality – questions about causality, confounding and methodology. *Addiction* 1995; **90**:493–498.
33 Skog O-J. Public health consequences of the J-curvehypothesis of alcohol problems. *Addiction* 1996; **91**:325–337.
34 Murray RP, Rehm J, Shaten J, Connett JE. Does social integration confound the relation between alcohol consumption and mortality in the Multiple Risk Factor Intervention Trial (MRFIT)? *J Stud Alcohol* 1999; **60**:740–745.
35 Poikolainen K. Inebriation and mortality. *Int J Epidemiol* 1983; **12**:151–155.
36 Kauhanen J, Kaplan GA, Goldgerg DE, *et al.* Frequent hangovers and cardiovascular mortality in middle-aged men. *Epidemiology* 1997; **8**: 310–314.
37 Dyer AR, Stamler J, Paul O, Berkson DM, Lepper MH, McKean H, Shekelle RB, Lindberg HA, Garside D. Alcohol consumption, cardiovascular risk factors, and mortality in two Chicago epidemiologic studies. *Circulation* 1977; **56**:1067–1074.
38 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**:201–213.
39 Rossow I, Amundsen A. Alcohol abuse and mortality: a 40-year prospective study of Norwegian conscripts. *Soc Sci Med* 1997; **44**: 261–267.
40 McElduff P, Dobson AJ. How much alcohol and how often? Population based case–control study of alcohol consumption and risk of a major coronary event. *BMJ* 1997; **314**:1159–1164.
41 Murray RP, Connett JE, Tyas SL, Bond R, Ekuma O, Silversides CK, Barnes GE. Alcohol volume, drinking pattern, and cardiovascular disease morbidity and mortality: is there a U-shaped function? *Am J Epidemiol* 2002; **155**:242–248.
42 Trevisan MT, Schisterman E, Mennotti A, Farchi, Conti S. Drinking pattern and mortality: The Italian Risk Factor and Life Expectancy Pooling Project. *Ann Epidemiol* 2001; **11**:312–319.
43 Wannamethee SG, Shaper AG. Alcohol and sudden cardiac death. *Br Heart J* 1992; **68**:443–448.
44 Wood D, De Backer G, Faegeman O, Graham I, Mancia G, Pyörälä K. Prevention of coronary heart disease in clinical practice. Recommendations of the Second Joint Task Force of European and Other Societies in Coronary Prevention. *Atherosclerosis* 1998; **140**:199–270.
45 Renaud SC, Ruf JC. Effects of alcohol on platelet function. *Clin Chim Acta* 1996; **246**:77–89.
46 Murray RP, Istvan JA, Daniels, Beaudoin CM. Alcohol and morbidity in the Lung Health Study. *J Stud Alcohol* 1998; **59**:250–257.
47 Bobak M, McKee M, Rose R, Marmot M. Alcohol consumption in a national sample of the Russian population. *Addiction* 1999; **94**:857–866.
48 Malyutina S, Bobak M, Kurilovitch S, Ryizova E, Nikitin Y, Marmot M. Alcohol consumption and binge drinking in Novosibirsk, Russia, 1985–1995. *Addiction* 2001; **96**:987–995.
49 Shkolnikov VM, Nemtsov A. The anti-alcohol campaign and variations in Russian mortality. In: Bobadilla JL, Costello CA, Mitchell F, editors. *Premature death in the new independent states.* Washington DC: National Academy Press; 1997. pp. 239–261.
50 Willich SN, Lowel H, Lewis M, Hormann A, Arntz HR, Keil U. Weekly variation of acute myocardial infarction. Increased Monday risk in the working population. *Circulation* 1994; **90**:87–93.
51 Chenet L, McKee M, Leon D, Shkolnikov V, Vassin S. Alcohol and cardiovascular mortality in Moscow; new evidence of a causal association. *J Epidemiol Community Health* 1998; **52**:772–774.
52 Evans C, Chalmers J, Capewell S, Redpath A, Finlayson A, Boyd J, *et al.* 'I don't like Mondays' – day of the week of coronary heart disease deaths in Scotland: study of routinely collected data. *BMJ* 2000; **320**: 218–219.
53 Trevisan M, Ram M, Hovey K, Rusell M, Freudenheim J, Muti P, *et al.* Alcohol drinking patterns and myocardial infarction. *Am J Epidemiol* 2001; S97.
54 Trevisan M, Krogh V, Farinaro E, Panico S, Mancini M. Alcohol consumption, drinking pattern and blood pressure: analysis of data from the Italian National Research Council Study. *Inter J Epidemiol* 1987; **16**: 520–527.
55 Wu T, Trevisan M. Drinking pattern and hypertension in a population-based sample. *Am J Epidemiol* 2001; **153**:s59.
56 Foppa M, Fuchs FD, Preissler L, Andrighetto A, Rosito GA, Duncan BB. Wine with the noon meal lowers post meal blood pressure: Randomized trial in centrally obese hypertensive patients. *Hypertension* 1999; **33**:119.
57 Hendriks HF, Veenstra J, Velthuis-te Wierik EJ, Schaafsma G, Kluft C. Effect of moderate dose of alcohol with evening meal on fibrinolytic factors. *BMJ* 1994; **308**:1003–1006.
58 Veenstra J, Ockhuizen T, van de Pol, Wedel M, Schaafsma G. Effects of moderate dose of alcohol on blood lipids and lipoproteins postprandially and in the fasting state. *Alcohol* 1990; **25**:371–377.
59 Gentry RT. Effect of food on the pharmacokinetics of alcohol consumption. *Alcohol Clin Exp Res* 2000; **24**:403–404.
60 Ramchandani VA, Kwo PY, Li TK. Effect of food and food composition on alcohol elimination rates in healthy men and women. *J Clin Pharmacol* 2001; **41**:1345–1350.
61 Bondy S, Rehm J. The interplay of drinking patterns and other determinants of health. *Drug Alcohol Rev* 1998; **17**:399–411.

62 Rimm EB, Klatsky A, Grobbe D, Stampfer M. Review of moderate alcohol consumption and reduced risk of coronary heart disease: is the effect due to beer, wine or spirits. *BMJ* 1996; **312**:731–735.
*Meta-analysis on beverage and CHD effects. Concluded that most of the protective effect is based on alcohol *per se* and not on any specific beverage.
63 Keil U, Chambless LE, Döring A, Filipiak B, Stieber J. The relation of alcohol intake to coronary heart disease and all-cause mortality in a beer-drinking population. *Epidemiology* 1997; **8**:150–156.
64 Bobak M, Skodova Z, Marmot M. Effect of beer drinking on risk of myocardial infarction: population based case–control study. *BMJ* 2000; **320**:1378–1379.
65 Reinke LA, McCay PB. Interaction between alcohol and antioxidants. In: Zakhari S, Wassef M, editors. *Alcohol and the cardiovascular system.* Bethesda, MD: National Institutes of Health, National Institute on Alcohol Abuse and Alcoholism; 1996. pp. 441–457.