The effects of different alcoholic drinks on lipids, insulin and haemostatic and inflammatory markers in older men

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Summary

Light to moderate drinking is associated with lower risk of coronary heart (CHD) than non-drinkers. We have examined the relationships between total alcohol intake and type of alcoholic beverage and several potential biological mechanisms.

We carried out the study in 3158 men aged 60-79 years drawn from general practices in 24 British towns with no history of myocardial infarction, stroke or diabetes and who were not on warfarin. Total alcohol consumption showed a significant positive dose-response relationship with high density lipoprotein cholesterol (HDL-C), coagulation factor IX, haematocrit, blood viscosity, and tissue plasminogen (t-PA) antigen, and an inverse dose-response relationship with insulin, fibrinogen, von Willebrand factor (vWF) and triglycerides after adjustment for possible confounders. Total alcohol consumption showed weak associations with plasma viscosity and fibrin D-dimer, and no association with factors VII, VIII, or C-reactive protein (CRP). Wine was specifically associated with lower CRP, plasma viscosity, factor VIII and triglycerides.

The findings are consistent with the suggestion that HDL-C in particular but also insulin and haemostatic factors may contribute to the beneficial effect of light to moderate drinking on risk of CHD. Wine has effects that may confer greater protection than other alcoholic beverages.

Keywords

Alcohol intake, haemostasis, insulin, lipids

Thromb Haemost 2003; 90: 1080–7

Introduction

It is well established that light to moderate alcohol consumption is associated with a lower risk of coronary heart disease (CHD) than observed in non-drinkers (1-3). Recent prospective studies suggest that this association is causal (3) but the precise mechanisms by which alcohol consumption reduces the risk of CHD remain uncertain. Lowering of HDL-cholesterol (HDL-C) is the best documented mechanism but only half of the protective effect appears to be mediated by HDL-C (4). Other mechanisms proposed include the effects of alcohol on insulin sensitivity, haemostasis and inflammation (3). Prospective studies have linked many of these variables including plasma insulin, fibrinogen, viscosity, C-reactive protein (CRP), tissue plasminogen activator (t-PA) antigen, fibrin D-dimer, von Willebrand factor (vWF) and factors VII and VIII to the risk of CHD (5-9). Although there have been several reports on the effects of alcohol on insulin (10-11) and fibrinogen (12-15), the effects of alcohol on other haemostatic variables are less well documented (3). Furthermore, some investigators have postulated that the

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Received April 10, 2003
Accepted after revision September 7, 2003

Financial support:
We thank the British Heart Foundation for project grant support.

DOI: 10.1160/TH03-04-0221

beneficial effect of alcohol is specific to or greater with wine, in particular red wine, suggesting that compounds other than ethanol may be of importance (1, 16). Whether all types of alcoholic beverage exert the same effect on these possible biological mechanisms is unclear. We therefore examined the effects of total alcohol intake and type of alcoholic beverage on several of the proposed biological mechanisms including plasma lipids, insulin, and haemostatic and inflammatory factors in a large population-based study of men aged 60-79 years.

Methods and subjects

The British Regional Heart Study is a prospective study of cardiovascular disease involving 7735 men aged 40-59 years selected from the age-sex registers of one general practice in each of 24 British towns, who were screened between 1978 and 1980 (17). Between 1998-2000, all surviving men, now aged 60-79 years, were invited for a 20-year follow-up examination. All men completed a questionnaire (Q20) providing information on their medical history, smoking and drinking habits, physical activity and occupation, had a physical examination, and provided a fasting blood sample. The men were also asked to fill in a separate questionnaire on dietary intake. The men were asked to fast for a minimum of 6 hours, during which they were instructed to drink only water and to attend for measurement at a pre-specified time between 08.00 h and 18.00 h. All men were asked to provide a blood sample, collected using the Sarstedt Monovette system. Of the 5565 surviving subjects, 4252 (77%) attended for examination and 4094 men (74%) had at least one measurement of the biological factors . We further excluded 134 men currently on warfarin and men with a recall of a diagnosis of myocardial infarction, stroke or diabetes (n = 760) leaving 3200 men.

Haemostatic and inflammatory variables

Blood was anticoagulated with K_2 EDTA (1.5 mg/ml) for measurement of haematocrit, white cell count and platelet count in an automated cell counter; and plasma viscosity at 37°C in a semi-automated capillary viscometer (Coulter Electronics). Blood viscosity was calculated from haematocrit and plasma viscosity as previously described (18). Blood was also anticoagulated with 0.109 M trisodium citrate (9 : 1 v : v) for measurement of clottable fibrinogen (Clauss method); as well as coagulation factors VII, VIII and IX in an MDA-180 coagulometer (Organon Teknika). Plasma levels of t-PA antigen and D-dimer were measured with enzyme linked immunosorbent assays (Biopool AB) as was von Willebrand factor (vWF) antigen (DAKO). C-reactive protein was assayed by ultra sensitive nephelometry (Dade Behring).

Serum lipids and insulin

Total cholesterol, HDL-C and triglycerides were measured using a Hitachi 747 automated analyzer using the methods of Siedel (19) and Sugichi (20) respectively. Low density lipoprotein-cholesterol values (LDL-C) were calculated using the Fredrickson-Friedwald equation. Serum insulin was measured using an ELISA assay which does not cross-react with proinsulin (21). LDL-C, triglycerides and insulin were adjusted for the effects of fasting duration and time of day (22).

Alcohol intake

Seven day recall

The men were asked to report the number of units of wine, beer and spirits consumed for each day of the week in the past 7 days as part of a dietary assessment. The men were classified into five groups based on their total intake: none, <1/day, 1-2/day, 3-4/day and >= 5 units/day. Intakes of beer, wine and spirits were also categorized quantitatively, but because of the small numbers in the higher categories, 2 or more drinks/day is the highest category for the individual types of beverages (none, <1/day, 1/day, >= 2/day). No information was obtained on red and white wine on the 7 day recall. Alcohol data were not available in 42 men. Seven day recall analyses are therefore based on 3158 men.

Standard questionnaire

Data presented in Table 3 were derived from the standard questionnaire in which the men were asked the total number of drinks/week and specifically if they had drunk red or white wine and the average number of glasses of wine drunk per week. No detailed information was obtained on the number of drinks of beer or spirits. These data relate to 1273 wine drinkers. The average number of drinks per week obtained from the standard questionnaire correlated very strongly with 7 day recall (r = 0.82).

Cardiovascular risk factors

Details of classification methods for smoking status, physical activity, body mass index and social class have been described (17, 25). Body mass index (BMI;weight/height^2 in kg/m^2) was calculated for each man at re-examination. 'Obesity' is defined as BMI $\geq$ 30 kg/m^2. Men with 'other' pre-existing CVD included men with a history of heart failure, "other heart trouble", aortic aneurysm, claudication, deep vein thrombosis or pulmonary embolism.

Statistical analysis

The distributions of white cell count, C-reactive protein and fibrin D-dimer were highly skewed and log transformation was used. Analysis of covariance was used to obtain adjusted mean levels for the alcohol categories. Standardised differences in Table 1 were calculated as the difference in mean divided by the standard deviation. Tests for linear trend for alcohol intake were assessed by assigning median values for the five alcohol intake groups and fitting alcohol as a continuous variable. Age and

	0 (655)	<1/day (687)	1-2/day (1145)	3-4/day (417)	5+/day (254)
Mean age	69.0	68.8	68.3	67.7	67.3
Mean BMI	26.3	26.7	26.8	26.8	27.1
% obese	12.4	14.6	16.0	13.0	19.3
% smokers	18.7	8.8	10.4	14.2	19.8
% active	36.8	46.6	54.8	56.6	47.3
% manual	64.7	55.0	45.4	51.1	54.3
% of total consumption as wine	0	35	30	23	13
% of total consumption as beer	0	44	46	56	66
% of total consumption as spirit	0	21	24	22	21

Table 1: Alcohol intake (7 day recall) and characteristics of men with no doctor diagnosis of myocardial infarction, stroke or diabetes.

BMI were fitted as continuous variables; physical activity, smoking and month of examination as categorical variables; and other pre-existing CVD as a dichotomous variable (yes/no).

Results

Table 1 shows some characteristics of the five alcohol groups. Alcohol was inversely associated with age and positively associated with BMI and obesity. Non-drinkers had similar smoking rates to the heaviest drinkers, with the lowest rates in lighter drinkers. Light and moderate drinkers tended to have the lowest rates of manual workers and the highest rates of physical activity.

Table 2 shows the mean levels for blood lipids, insulin and the haemostatic and inflammatory factors adjusted for age, BMI, smoking, physical activity, social class and "other" pre-existing CVD. Total alcohol consumption was significantly and positively associated with HDL-C, factor IX, t-PA, haematocrit and blood viscosity and was significantly and inversely associated with triglycerides, serum insulin levels, white cell count, fibrinogen and von Willebrand Factor, and to a weaker extent with plasma viscosity and fibrin D-dimer. There was little difference in LDL-C between those drinking up to 4 drinks/day, but heavy drinkers had significantly lower levels than the other groups. No association was seen with CRP, coagulation factor VII or factor VIII. Further adjustment for month of screening (as a proxy for temperature) made little difference to the relationships seen (data not shown). For comparative purposes, standardized differences in mean were calculated to compare the effects of moderate drinking (3-4 drinks/day) on the biolog-

Table 2: Alcohol intake (7 day recall) and adjusted mean levels of blood lipids, insulin, haemostatic and inflammatory variables in men with no doctor diagnosis of myocardial infarction, stroke or diabetes.

	0 (655)	<1/day (687)	1-2/day (1145)	3-4/day (417)	≥5/day (254)	test for trend ##	Standardized Difference moderate (3-4/day) vs none
HDL-Cholesterol (mmol/L)	1.26	1.27	1.35	1.42	1.58	*p<0.0001*	+0.47
LDL-Cholesterol (mmol/L)	3.92	4.04	3.99	3.95	3.81	*P=0.04*	+0.03
Triglycerides (mmol/L)+	1.64	1.60	1.59	1.57	1.48	*P=0.006*	- 0.08
Insulin + (mU/l)	8.58	8.24	7.85	7.69	7.24	*P<0.0001*	- 0.19
Privat White cell count (10^9/L) +	6.89	6.75	6.69	6.69	6.59	*P=0.02*	- 0.11
C-reactive protein (mg/L) +	1.75	1.63	1.58	1.63	1.67	*NS*	- 0.06
Hct (%)	44.94	44.94	45.24	45.39	45.86	*P<0.0001*	+13.3
Plasma viscosity (mPa.s)	1.288	1.283	1.278	1.277	1.281	*p=0.09*	- 0.14
Blood viscosity (mPa.s)	3.39	3.38	3.39	3.40	3.45	*p=0.004*	+0.03
Clottable fibrinogen (g/L)	3.30	3.26	3.22	3.19	3.08	*p<0.0001*	- 0.15
Factor VII (iu/dl)	118.8	119.6	120.0	118.9	121.5	*NS*	+0.04
Factor VIII (iu/dl)	130.7	130.8	130.4	130.6	131.4	*NS*	- 0.03
Factor IX (iu/dl)	130.0	132.2	133.0	135.2	137.5	*p<0.0001*	+0.23
VWF (iu/dl)	139.8	137.9	135.6	133.2	133.5	*p=0.01*	- 0.15
t-PA (ng/ml)	10.50	10.16	10.77	11.48	12.15	*p<0.0001*	+0.23
D-dimer (ng/ml) +	82.3	85.6	79.8	80.6	76.7	*p=0.07*	- 0.03

+ geometric mean used

trend adjusted for age, BMI, smoking, social class, physical activity and 'other' pre-existing CVD disease.

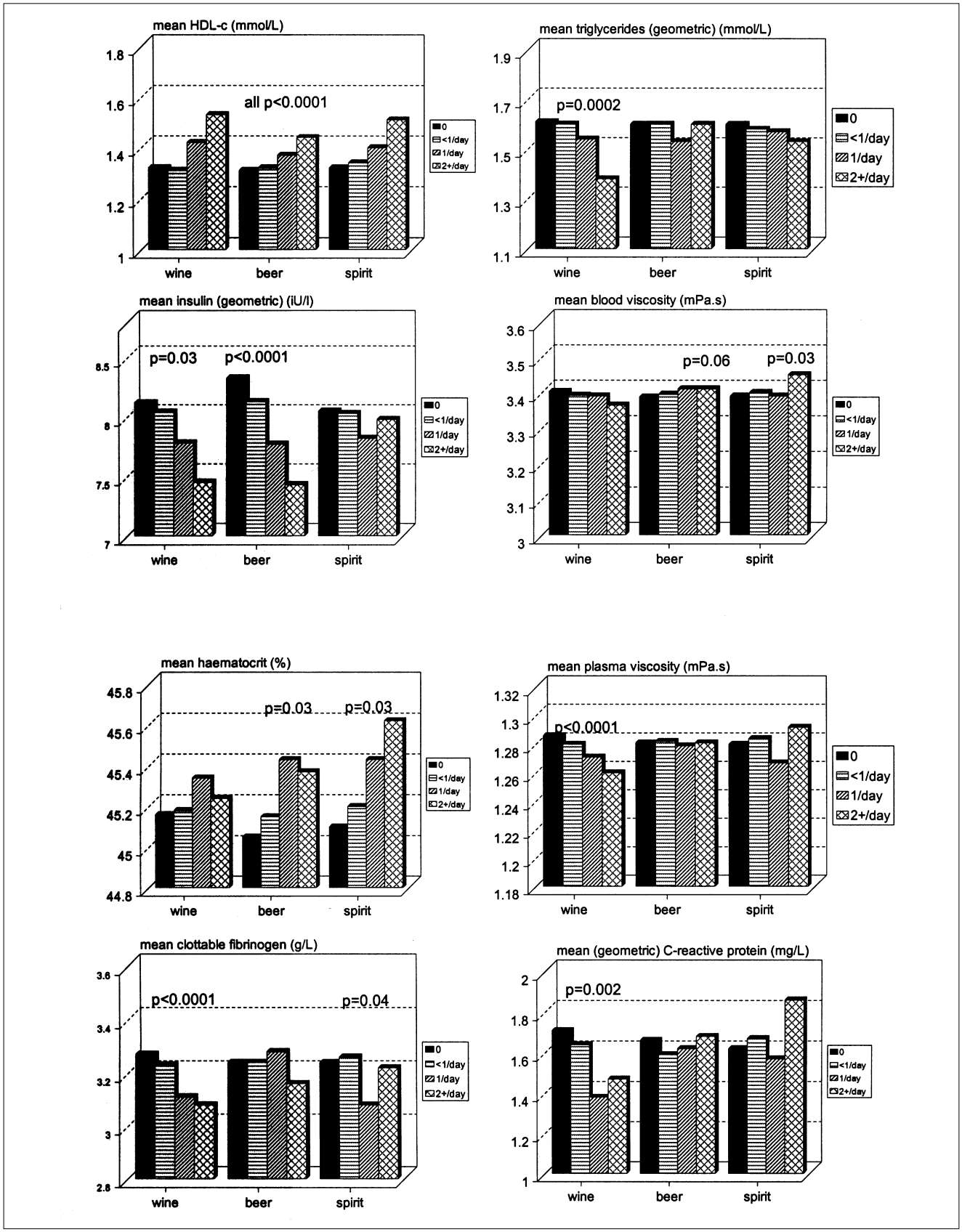

Figure 1: Type of alcoholic beverage and adjusted mean levels of blood lipids, insulin and haemostatic and inflammatory markers. Adjusted for age, BMI, smoking, social class, physical activity and 'other' pre-existing CVD disease.

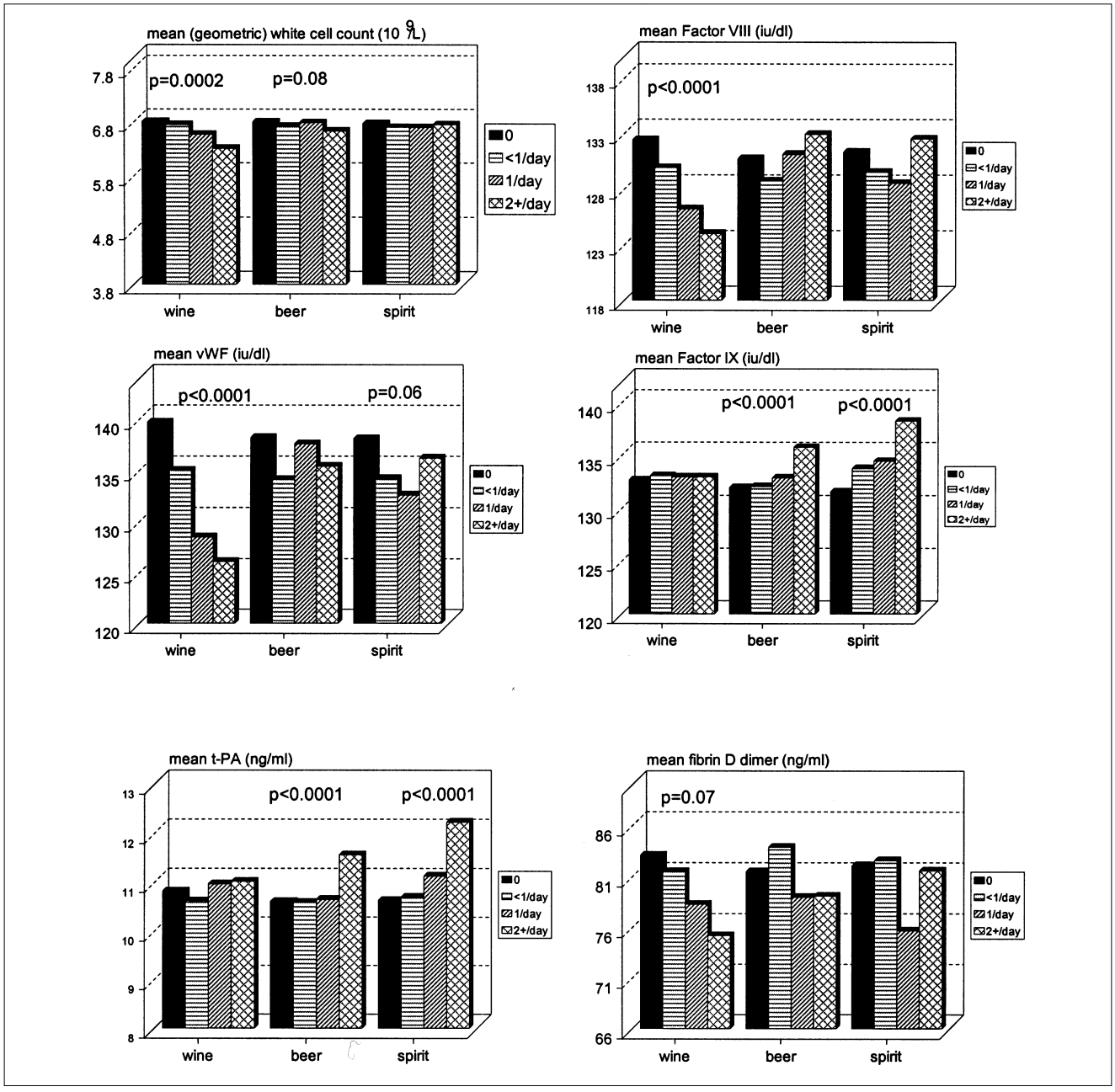

Figure 1: continued

ical markers (Table 2). The strongest association by far was seen for HDL-C, with more moderate associations with t-PA, factor IX, insulin and fibrinogen.

Type of alcoholic beverage and biological markers

Beer was the most popular type of beverage consumed; 57% reported drinking beer, 43% wine and 41% spirits. The average total alcohol consumption was 15.5 units/week for wine drinkers, 18.3 units/week for beer drinkers and 17.3 units/week for those reporting spirit drinking. The relationship between alcohol and the biological markers was examined by type of beverage, adjusting for factors in Table 2. Only factors that showed a significant or marginally significant association with at least one of the alcoholic beverages are presented (Fig. 1). Tests for trend for each beverage type which are significant, or of marginal significance are indicated on the figure. Because of the smaller numbers involved we are primarily interested in the difference in patterns rather than the statistical significance of the trend within each group.

Table 3: Adjusted mean levels of cardiovascular risk factors , haemostatic and inflammatory markers in 1273 wine drinkers based on usual weekly average intake. Adjusted for age, BMI, smoking, social class, physical activity, 'other' pre-existing cardiovascular disease and total average weekly alcohol intake.

	White wine (269)	Red wine (386)	Red+white (618)	Red vs white p-value
Average wine	3.0 drinks	5.7 drinks	7.1 drinks	
Average total	7.4 drinks	12.4 drinks	12.3 drinks	
HDL-C (mmol/L)	1.34	1.38	1.38	*P=0.06*
Triglyceride (mmol/L)+	1.54	1.55	1.52	*NS*
LDL-C (mmol/L)	4.00	4.08	4.02	*NS*
Insulin (mU/l)+	7.8	7.7	7.9	*NS*
Hct (%)	45.20	45.21	45.40	*NS*
Blood viscosity (mPa.s)	3.39	3.37	3.38	*NS*
White cell count (10^9/L)+	6.69	6.45	6.49	*P=0.05*
C-reactive protein (mg/L)+	1.55	1.35	1.32	*P=0.04*
Clottable fibrinogen (g/L)	3.21	3.12	3.09	*P=0.03*
Plasma viscosity (mPa.s)	1.274	1.268	1.267	*NS*
Factor VIII (iu/dl)	125.2	126.2	126.8	*NS*
Factor IX (iu/dl)	132.06	132.9	130.5	*NS*
VWF (iu/dl)	133.8	127.3	129.8	*NS*
t-PA (ng/ml)	10.7	10.3	10.4	*NS*
D-dimer (ng/ml)+	79.0	72.2	71.5	*P=0.05*

+geometric mean used

Blood lipids and insulin

Strong positive associations were seen with HDL-C for all beverage types (Fig. 1). The inverse association with triglycerides was only seen with wine drinking. The inverse relationship with insulin was most apparent with wine and beer drinking; a lesser effect was seen for spirits. No consistent relationship was seen between LDL-C and the type of alcoholic beverage (data not shown).

Haemostatic and inflammatory markers

Only wine consumption was inversely associated with plasma viscosity and the inverse association seen between total alcohol and fibrinogen was most consistent for wine. Although no association was seen between total alcohol consumption and CRP, wine consumption was significantly and inversely related to CRP, as well as white cell count. Beer consumption showed only a weak relationship with white cell count, and consumption of spirits showed no relationship with the inflammatory markers. By contrast, the positive associations between total alcohol and haematocrit, blood viscosity, factor IX and t-PA were only seen for beer and spirits. The inverse relationship with vWF was seen for all beverage types, but was most marked in wine drinkers. Only wine consumption showed a significant inverse relationship with factor VIII. For fibrin D-dimer, weak inverse relationships was seen for all beverage types.

Red wine versus white wine

We compared the effects of red and white wine consumption among 1273 men who reported drinking at least one glass of wine a week on average. Men who reported red wine drinking had significantly higher total consumption than men who drank only white wine. Table 3 shows the mean levels of the biological factors, adjusted for factors in Table 2 as well as for total alcohol consumption. Men who reported drinking red wine (red wine only and red and white wine) showed significantly lower mean levels of fibrinogen and CRP than men who reported only white wine; and lower levels of HDL-C, white cell count and fibrin D-dimer, but these associations were of marginal significance.

Discussion

Earlier prospective findings from the British Regional Heart study have shown light and moderate drinking to be associated with about a 20% reduction in risk of major CHD events (fatal and non-fatal) compared to occasional drinkers (<1 unit/week) (24). In the present cross sectional cohort total alcohol consumption was significantly and favourably associated with several factors associated with risk of CHD including HDL-C (positively), insulin (inversely) and haemostatic and inflammatory factors such as fibrinogen, vWF, white cell count and to a lesser extent plasma viscosity and fibrin D-dimer (inversely) suggesting that these may be possible mechanisms by which total alcohol may lower CHD. Total alcohol consumption was most strongly and positively associated with increased HDL-C. This was seen for all types of beverage, in agreement with other studies, suggesting that this effect is due to ethyl alcohol itself (25). The inverse relationship between total alcohol consumption and insulin as seen in other studies (10, 11) was most

marked in beer and wine drinkers and is consistent with the reported finding of a stronger inverse association between light to moderate drinking and risk of type 2 diabetes in beer and wine drinkers (26).

Type of beverage and haemostatic and inflammatory markers

We observed differing effects of alcoholic beverage (beer, wine, spirits) on several of the haemostatic and inflammatory variables as has been reported in other studies (14, 15).

The inverse relationship between alcohol consumption and fibrinogen was most marked with wine drinking suggesting that alcohol amount as well as other components in wine might influence fibrinogen levels. While a strong dose response relationship was seen with fibrinogen the association of alcohol consumption with plasma viscosity was weaker and the lowering effects of alcohol on plasma viscosity appeared to be specific to wine, which may account for the inconsistent associations seen between studies (12, 13). By contrast, total alcohol consumption was positively associated with haematocrit and blood viscosity, but this was only seen for beer and spirits.

It has been suggested that alcohol may have anti-inflammatory actions which could contribute to the lower CHD risk associated with moderate drinking (27). The relationship between alcohol and CRP was only seen for wine and suggests that wine has properties which reduce inflammatory markers, and further analyses comparing red and white wine suggest that this may be specific to red wine.

A significant inverse relationship was seen between total alcohol intake and vWF as reported in previous studies (13) but not with factor VIII despite its high correlation with vWF. The lowering effect on vWF was strongest for wine. A raised vWF concentration has been proposed as an indicator of endothelial dysfunction (28) and has been associated with increased risk of CHD (9). vWF may be another mechanism by which light to moderate drinking may be protective against CHD. Wine consumption exerted a strong negative effect on factor VIII, while beer and spirit consumption showed small but non-significant positive relationships. Hence wine consumption may lower plasma levels of the vWF-factor VIII complex, perhaps as an "anti-inflammatory" effect, as seen for fibrinogen, CRP, plasma viscosity and white cell count. By contrast total alcohol intake showed strong positive relationships with factor IX that was not seen with wine. There are few reports of factor IX and risk of CHD, although it may have a potential role in thrombogenesis as shown by infusion studies and its associations with venous thromboembolism (29) It is possible that the greater effect of wine consumption in lowering CHD risk may reflect not only its anti-inflammatory effects, but also its lack of prothrombotic effects of raised factor IX levels.

Prospective studies have shown positive associations between t-PA and risk of CHD (6) and ischaemic stroke (30) and increased level of t-PA-PAI-1 complexes has been associated with haemorrhagic stroke (31). The strong positive association seen between total alcohol consumption and t-PA antigen (less apparent with wine) seen in this and other studies (12, 32) suggests that t-PA may be one of the mechanisms by which alcohol influences haemorhagic stroke.

Red versus white wine

Some studies have suggested that red wine is more protective than white wine (16). There is some evidence that resveratrol and other polyphenolic compounds found in red wine can have an independent and additive effect on the inhibition of platelet aggregation (33). The number of men who drank only white wine in this study was small and with few exceptions there was little difference in the level of biological markers between red and white wine. Red wine appeared to have a greater effect on fibrinogen than white wine and the significantly lower levels of CRP among red wine drinkers compared to white wine suggest that red wine may have anti-inflammatory properties.

Limitations

Several studies have observed that wine drinkers had healthier diets than those who preferred beer or spirits (34, 35). While there remains a possibility that the differences in effects may be due to differences in dietary habits, the effects of diet on haemostatic factors are not yet well established.

Type of beverage and risk of CHD

It has often been argued that the greater protective effect of wine on CHD seen in some studies may be due to the confounding effects of health lifestyle factors (36). A recent meta analysis showed strong associations for both beer and wine at levels of moderate consumption but a stronger inverse association for wine (32% risk reduction) than beer (22%) (1). In previous reports from this cohort, light to moderate drinkers showed lower risk of major CHD than non and occasional drinkers and wine drinkers showed lower CHD rates than beer or spirit drinkers (24, 36). The general finding that all alcoholic beverages are protective is consistent with the favourable effects of alcohol on HDL-C seen for all beverage types. The findings of greater or specific effect of wine compared to beer and spirits on several of the haemostatic and inflammatory markers suggest that the apparent greater protective effect of wine on CHD may be real. The greater protection from CHD by wine (1) may be linked to its components which have more favourable effects on haemostatic and inflammatory variables compared to other types of alcoholic drinks and the advantage appears to be greater for red wine. This paper only addresses the effects of alcohol on possible mechanisms which may lower CHD. It is evident that the major mechanism for CHD affected by alcohol is the HDL-cholesterol concentration, which probably accounts for much of the protective effect associated with light/moderate alcohol intake.

Whether the effects of different types of alcohol on the other biological factors such as insulin, fibrinogen, vWF and CRP reported in this and other studies account for any additional benefit for CHD risk is yet to be established.

Acknowledgements

The British Regional Heart Study is a British Heart Foundation Research Group and is also supported by the Department of Health, England.

The views expressed in this publication are those of the authors and not necessarily those of the Department of Health (England).

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