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Overall alcohol intake, beer, wine, and systemic markers of inflammation in western Europe: results from three MONICA samples (Augsburg, Glasgow, Lille)

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Aim Anti-inflammatory effects of moderate alcohol consumption have been proposed to explain why moderate alcohol intake lowers coronary heart disease risk. We investigated the relationship between overall alcohol, beer or wine consumption and markers of systemic inflammation in three different geographical areas in Europe.
Methods and results Cross-sectional samples, each representative of the general population from Germany, Scotland, and France (MONICA Augsburg 1994/95, 2275 men and 2186 women, 25–74 years; Glasgow MONICA 1994/95, 561/616, 25–74 years, and MONICA Lille 1994/95, 581/574, 35–64 years) were studied. Alcohol intake was assessed by standardized interview. Adjusted means of C-reactive protein (CRP), fibrinogen, white blood cell (WBC) count, plasma viscosity (PV), and albumin were calculated among categories of alcohol intake, and separately for beer or wine consumption, by multiple linear regression. Self-reported moderate daily alcohol intake up to 40 g was associated with lower concentrations of CRP, fibrinogen, PV and WBC count, compared to non-drinking and heavy drinking, even after adjustment for various potential confounders.
Conclusions Moderate consumption of either wine or beer is associated with lower levels of systemic inflammatory markers in three different European areas, suggesting that ethanol itself might be largely responsible for the potential anti-inflammatory effects of these beverages.

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Introduction

Moderate alcohol intake has consistently been shown to be associated with lower risk for fatal and non-fatal cardiovascular disease (CVD).[1] The lower CVD risk in moderate consumers of alcohol has been observed in apparently healthy subjects,[2] in patients with diabetes,[3] or hypertension[4] and in those with prior myocardial infarction (MI).[5] It has been suggested that favourable changes in blood lipids and in the haemostatic profile, or reduced insulin resistance might mediate the atheroprotective effect of moderate alcohol.[6,7] Atherosclerosis is an inflammatory disease, characterised by local inflammation in the vessel wall[8] but also shows a systemic, low-grade response as indicated by elevated C-reactive protein (CRP), total white blood cell (WBC) count, fibrinogen and plasma viscosity (PV), and decreased albumin. All these markers have consistently been associated with increased risk of cardiovascular disease.[9–12]

Acute, as well as chronic, alcohol consumption is known to affect the innate immune system as well as the adaptive immune response.[13] Recently, we reported lower concentrations of several markers of inflammation, including CRP, among moderate consumers of alcohol in a large representative sample of the general population of former West Germany and suggested that an anti-inflammatory action of moderate amounts of alcohol might represent an additional mechanism that mediates decreased CVD risk.[14] These findings have been confirmed in other population-based samples for CRP and WBC count, in individuals with and without pre-existing CVD[15–17] and most recently for IL-6.[18] In addition, in a small cross-over study, Sierksma et al.[19] demonstrated a significant reduction of CRP concentrations and fibrinogen after 3 weeks of diet- controlled consumption of 4 (men) or 3 (women) glasses of beer. The aim of the present study was to assess the relationship between alcohol consumption and systemic markers of inflammation in three European countries with markedly different CVD risk and differing social background, and also different patterns of alcohol consumption.

Material and methods

Study populations and data collection

Three cross-sectional samples, randomly drawn from the general population of areas of Germany (Augsburg), France (Lille), and Scotland (Glasgow) giving a total of 7887 men and women, were examined. Participants with complete data sets for the respective inflammatory marker and all covariates were included thus leaving 6787 (CRP), 5778 (fibrinogen), 5614 (WBC count), 5765 (PV), and 5778 (albumin) individuals for analyses. All these were multinational monitoring of trends and determinants in cardiovascular disease (MONICA) surveys, carried out in 1994/95. The original MONICA Augsburg sample consisted of 2405 men and 2451 women aged 25–74 years, the Lille sample consisted of 601 men and 594 women aged 35–64 years and the Glasgow sample consisted of 865 men and 971 women aged 25–74. There were no substantial differences between the original samples and the analysed samples according to potential confounders. Participants were submitted to the same standardized interview, carried out by trained personnel, including questions reporting medical history, life-style, and drug history. Blood pressure, body height (in metres), body weight (in kilograms), body mass index and smoking behaviour were determined according to the MONICA protocol.[20]

Alcohol consumption

For estimation of alcohol consumption in the MONICA Augsburg sample, each subject was asked how much beer, wine, and spirits he or she had drunk on the previous workday and over the last weekend. Total alcohol intake was calculated by multiplying weekday consumption by five and adding this figure to weekend consumption. After conversion (1 litre beer = 40 g, 1 litre wine = 100 g, 0.02 litre spirits = 6.2 g alcohol) an average amount of alcohol intake in grams per day was derived. This recall method was validated in a subsample of 899 male participants of the first MONICA Augsburg survey in 1984/85, who additionally completed a seven-day dietary record. The average of overall alcohol intake in this subsample was 35.5 g/day for the recall method and 34.7 g/d for the dietary method, 6.2/6.4 g/d for alcohol intake by wine, 28.1/26.8 g/d for beer, and 1.2/1.6 g/d for spirits, respectively, suggesting reasonable agreement.[21]

In Glasgow MONICA, data on alcohol intake were collected by a seven-day recall. For each day, the number of pints of beer or low-alcohol beer, glasses of wine or measures of spirits were collected. Then these data were converted into standard units (1 pint of beer, lager, shandy = 2 units, 1 glass of wine or one measure of spirits = 1 unit) and daily average consumption was calculated. For low-alcohol beer, 2/3 of a unit was allocated to 1 pint. The conversion factor used for calculation of absolute alcohol per unit (1 unit = 10 ml) was 0.8.

Estimation of alcohol consumption in the MONICA Lille sample was assessed by a quantitative frequency questionnaire, detailing every day of the week, every type of alcoholic beverages and being representative of the 12 last months. Drinking habits were then translated into millilitre of ethanol per week, using the mean of quantity consumed each day and the alcohol content of the drink. In modelling, total alcohol intake was expressed as the sum of millilitre of ethanol per week from wine, beer and cider, and spirits. The conversion factor used for calculation of absolute alcohol per unit was 0.8.

Laboratory methods

According to the MONICA protocol, non-fasting blood was drawn in sitting position from an antecubital vein after short occlusion with minimal suction. WBC count was determined from whole blood immediately after collection.[20] All other samples (plasma for CRP, fibrinogen, albumin, lipids, and viscosity) were stored at −70 °C until analysis. CRP measurements for all three samples were performed by a high-sensitivity immunoradiometric assay (range 0.05–10 mg/l), calibrated with the WHO standard 85/506.[22] Co-efficient of variation (CV) for CRP measurement across the whole range of values was 12%. Fibrinogen and albumin concentrations were determined by an immunonephelometric assay run on a BN II Analyzer (Dade Behring, Marburg, Germany). CVs for fibrinogen and albumin concentrations were 4.9% and 6.8%, respectively. PV was determined by a Harkness coulter capillary viscosimeter (CV 0.9%).[23] All analyses were done in the same laboratory in a blinded manner. WBC counts and lipids were determined by laboratory methods according to the MONICA standard in each centre. Values were missing if blood was not available at all, because of insufficient sample volume or if measurements were not part of the protocol for the respective study centre.

Statistical analyses

Demographic, clinical, and biochemical characteristics are shown in a descriptive way for each sample and, for the pooled sample, in categories of alcohol intake. Throughout, moderate alcohol consumption is used for consumption of up to 40 g of alcohol per day. Because of their skewed distribution, CRP concentrations are expressed as geometric means or as medians together with their interquartile ranges. All other parameters are reported as arithmetic means together with their standard deviations (SD) or as numbers and proportions. The v^2 test and ANOVA were used to assess crude differences between categories of alcohol intake. Adjusted geometric means for CRP (by using log CRP in the model) and adjusted arithmetic means for the other inflammatory markers were calculated in categories of daily alcohol intake from multiple linear regression analyses. Known or presumed potential confounders including age (four categories), sex, smoking status (current, ex, never), body mass index (continuous), total cholesterol (continuous), formal education ($\leqslant$8 years, 9—11, >11 years), physical activity (two categories), hypertension (three categories), history of diabetes (yes/no), history of ischaemic heart disease (yes/no), treatment with aspirin (yes/no) or lipid-lowering drugs (yes/no) were forced into all models. When a linear relation between a covariate and the dependent variable was detected in univariate analyses, the covariate was used as a continuous variable in the regression model, except for age because of differing age ranges.

Analyses were performed on each sample first and then for the pooled sample, separately for men and women, and further according to type of beverage exclusively consumed. For assessment of a potential non-linear relationship between alcohol consumption and concentrations of inflammatory markers, alcohol consumption was included as a continuous variable: first as a linear term only, and then as a linear and quadratic term. All comparisons between alcohol categories in the pooled sample are adjusted for study centre including two dummy variables. Throughout, subjects classified as non-drinkers served as the reference group. All tests performed were two-sided, and a p-value <0.05 was considered statistically significant. All computations were performed using SAS software, Release 8.2 (SAS Institute Inc. Cary, NC, USA).

Results

Clinical and biochemical characteristics of the study populations are presented in Table 1. Participants of Glasgow MONICA were more frequently smokers and reported less alcohol intake, compared to the Augsburg and Lille subjects. Other clinical characteristics were not appreciably different between the three locations. Mean CRP concentrations were similar among all samples; fibrinogen, HDL- and total cholesterol concentrations were higher in Augsburg compared to Glasgow whereas PV and albumin were higher in Glasgow. However, participants from Lille had the highest levels of HDL-cholesterol. Conversely, WBC count was lower in Lille than in Augsburg. Overall alcohol consumption was highest in Lille. Men reported to drink substantially more than women. Male participants in Lille preferably consumed wine but beer was preferred in Augsburg and Glasgow. Consumption of spirits was sporadic among all participants (data not shown). Those consuming >0—20 g and >20—40 g in the Augsburg and Glasgow sample and those consuming >0—20 g of alcohol per day in Lille were younger than non-drinkers and those consuming >40—80 g/d. Body mass index was lowest among those consuming >20 g/d. The proportion of those attending less than 10 years of formal school education was highest among non-drinkers.

In Table 2, crude clinical and biochemical characteristics of pooled study samples were presented as proportions, as arithmetic means and their standard deviation or as geometric means together with corresponding 95% confidence interval by category of alcohol intake. Proportions of males and current smokers, as well as means of systolic and diastolic blood pressure, increased with increasing alcohol intake (Table 2). In crude analyses, concentrations of all positive markers of inflammation were lower among moderate consumers of alcohol, compared to non-drinkers and heavy drinkers. For albumin concentrations the opposite was true (Table 2).

Adjustment for various potential confounders did not substantially attenuate this relationship between inflammatory markers and reported alcohol consumption (Table 3).

Further analyses separately performed for men and women in the pooled sample and by type of beverage consumed suggest that there are no substantial gender effects and furthermore, that the association observed is marginally more pronounced for CRP and WBC count among those who reported exclusively consumption of wine compared to beer (Fig. 1).

Discussion

In the present analysis of large samples, representative of the general populations from three European countries, we observed lower plasma concentrations of several systemic biomarkers of inflammation among consumers of moderate amounts of alcohol, compared to non-drinkers and heavy drinkers. Adjustment for various potential confounders did not appreciably alter these results and the findings were consistent among all three samples, and in the pooled sample among men, but less strong in women. Moreover, the association was seen in both those who reported exclusive wine or beer consumption, with a somewhat more pronounced effect on CRP and WBC count among drinkers of wine.

Alcohol, CHD, and systemic markers of inflammation

A large number of epidemiological and clinical studies have consistently documented that increased levels of several systemic markers and regulator proteins of the acute phase response, and lower levels of albumin, are associated with cardiovascular endpoints.[9—12] Recently, anti-inflammatory mechanisms have been suggested to contribute to the beneficial effect of moderate alcohol

Table 1 Clinical and biochemical characteristics of study samples[a]

	Augsburg	Glasgow	Lille	p[c]
Number				
Original sample	*4856*	*1836*	*1195*	
Analysed sample[b]				
CRP	*4461*	*1173*	*1153*	
Fibrinogen	*4480*	*1298*		
Plasma viscosity	*4470*	*1295*		
Albumin	*4480*	*1298*		
WBC	*4467*		*1147*	
Clinical risk factors				
Age [years]	**49.8** (14.0)	**45.3** (11.5)	**51.3** (8.4)	<0.0001
Male [*N* (%)]	**2275** (51.0)	**760** (47.2)	**579** (50.2)	0.09
Body mass index [kg/m^2]	**27.0** (4.5)	**26.3** (4.9)	**26.6** (5.0)	<0.0001
Current smokers [it N (%)]	**1138** (25.5)	**658** (41.2)	**279** (24.2)	<0.0001
SBP [mmHg]	**133** (20)	**128** (19)	**134** (19)	<0.0001
DBP [mmHg]	**80** (11)	**78** (12)	**83** (11)	<0.0001
History of heart disease [*N* (%)]	**136** (2.9)	**62** (3.9)	**40** (3.5)	0.18
Diabetes [*N* (%)]	**210** (4.5)	**33** (2.1)	**59** (5.1)	<0.0001
Aspirin [*N* (%)]	**246** (5.3)	**114** (7.1)	**47** (4.1)	<0.0001
Lipid-lowering drugs [*N* (%)]	**152** (3.3)	**9** (0.6)	**139** (12.1)	<0.0001
Physically inactive [*N* (%)]	**1553** (33.4)	**600** (37.2)	**215** (18.6)	<0.0001
Education [years][d]	**10** (10–12)	**11** (10–13)	**10** (8–13)	<0.0001
Daily alcohol intake [g][d]				
Overall				
Men	**20.0** (3.1–40.0)	**16.7** (3.9–34.7)	**29.6** (10.7–56)	<0.0001
Women	**1.8** (0–11.4)	**1.3** (0–9.0)	**6.1** (0–20.0)	<0.0001
Wine				
Men	**0** (0–2.9)	**0** (0–0)	**12.0** (1.1–32.0)	
Women	**0** (0–2.9)	**0** (0–0)	**1.6** (0–8.2)	
Beer				
Men	**14.3** (0–28.6)	**8.0** (0–22.5)	**3.2** (0–13.8)	
Women	**0** (0–1.3)	**0** (0–0)	**0** (0–2.6)	
Laboratory variables				
CRP [mg/l][d]	**1.38** (0.63–2.96)	**1.30** (0.62–3.26)	**1.30** (0.65–3.21)	0.27
Fibrinogen [g/l]	**2.90** (0.71)	**2.65** (0.61)		<0.0001
Plasma viscosity [mPa s]	**1.226** (0.06)	**1.275** (0.07)		<0.0001
WBC count [10^9/l]	**7.15** (1.90)		**6.48** (1.86)	<0.0001
Albumin [g/l]	**43.4** (4.6)	**44.8** (4.3)		<0.0001
HDL [mmol/l]	**1.40** (0.43)	**1.34** (0.39)	**1.50** (0.48)	<0.0001
TC [mmol/l]	**5.98** (1.15)	**5.89** (1.13)	**5.90** (1.08)	0.07

CRP indicates C-reactive protein; WBC, white blood cell count; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein; TC, total cholesterol.
[a] Given as arithmetic mean with standard deviation or numbers and proportions if not otherwise noted.
[b] Numbers of individuals with complete data sets for all covariates in regression analyses, distributions of covariates are given for the subsample.
[c] p for difference between samples.
[d] Median and interquartile range.

consumption on CHD risk beyond favourable changes in lipids and haemostatic factors.[14–16,19] However, reports on potential anti-inflammatory effects of moderate alcohol consumption in samples from the general population from Europe are scarce. Moreover, findings on potentially differing effects of different types of alcoholic beverages have not been reported so far. In the present study, we were able to confirm lower levels of pro-inflammatory markers among consumers of moderate amounts of alcohol in samples representative of populations at high (Glasgow), and intermediate risk (Augsburg, Lille) for CHD, irrespective of potential confounders, such as life-style habits or social background.

Potential interaction of alcohol with inflammation in atherosclerosis

Alcohol has been shown to suppress the synthesis of pro-inflammatory cytokines and chemokines (such as TNF-α, IL-1β, IL-6, IL-8, and MCP-1), both in vivo and in vitro, in alveolar macrophages and human blood monocytes.[24–27] This suggests a decrease of acute phase reactants after alcohol ingestion, since e.g. IL-6 is the principal regulator of the genes encoding for most of the acute phase reactants.[28]

In isolated human monocytes ex vivo treated with ethanol, downregulation of nuclear transcription factor-κB

Table 2 Crude clinical and biochemical characteristics of pooled study samples according to alcohol consumption

Daily alcohol intake [g]	0	>0—20	>20—40	>40—60	>60—80	>80	p[a]
Number[b]	*2001*	*2678*	*1126*	*537*	*265*	*184*	
Clinical risk factors							
Age [years]							
Augsburg	**50.2** (14.2)	**49.1** (14.1)	**48.8** (14.0)	**49.8** (12.6)	**50.1** (12.9)	**48.3** (11.6)	0.16
Glasgow	**45.9** (11.9)	**44.4** (11.7)	**43.3** (11.1)	**45.3** (10.3)	**45.4** (10.6)	**43.2** (9.4)	0.23
Lille	**51.4** (14.2)	**50.2** (14.2)	**51.8** (14.2)	**51.8** (14.2)	**52.9** (14.2)	**53.0** (14.2)	0.01
Male [%]	**29.9**	**43.2**	**69.5**	**86.0**	**90.2**	**95.6**	<0.0001
Body mass index [kg/m^2]	**27.4** (5.5)	**26.3** (4.3)	**26.6** (4.0)	**27.2** (4.4)	**27.2** (3.8)	**26.6** (4.1)	<0.0001
Current smokers [%]	**25.2**	**24.8**	**28.0**	**38.4**	**43.0**	**53.9**	<0.0001
SBP [mmHg]	**130** (20)	**130** (19)	**133** (18)	**137** (18)	**141** (20)	**142** (21)	<0.0001
DBP [mmHg]	**79** (12)	**79** (11)	**82** (11)	**84** (11)	**86** (12)	**87** (13)	<0.0001
History of heart disease [%]	**3.4**	**2.6**	**2.8**	**3.6**	**3.8**	**4.5**	0.38
Diabetes [%]	**6.0**	**3.3**	**3.3**	**3.2**	**3.4**	**5.6**	<0.0001
Aspirin [%]	**10.0**	**8.7**	**8.5**	**7.4**	**6.0**	**6.1**	0.12
Lipid-lowering drugs [%]	**3.7**	**3.7**	**4.3**	**4.8**	**8.3**	**6.7**	0.004
Physically inactive [%]	**36.9**	**30.5**	**25.6**	**25.1**	**29.1**	**27.2**	<0.0001
Education <10 years [%]	**19.2**	**11.1**	**7.2**	**7.0**	**7.0**	**4.4**	0.01
HDL cholesterol [mmol/l]	**1.35** (0.41)	**1.42** (0.43)	**1.41** (0.44)	**1.40** (0.39)	**1.43** (0.47)	**1.52** (0.57)	<0.0001
Inflammatory markers							
CRP [mg/l][c]	**1.63** (1.55—1.72)	**1.25** (1.19—1.30)	**1.26** (1.17—1.34)	**1.45** (1.32—1.60)	**1.57** (1.37—1.82)	**1.65** (1.39—1.95)	0.0001
Fibrinogen [g/l]	**3.01** (0.74)	**2.80** (0.67)	**2.69** (0.62)	**2.77** (0.66)	**2.78** (0.61)	**2.88** (0.75)	0.0001
Plasma viscosity [mPa s]	**1.244** (0.07)	**1.232** (0.07)	**1.231** (0.06)	**1.231** (0.07)	**1.246** (0.07)	**1.261** (0.06)	0.0001
WBC count [10^9/l]	**7.13** (2.0)	**6.91** (1.9)	**6.87** (1.7)	**7.06** (1.9)	**7.16** (2.0)	**7.37** (2.1)	0.0004
Albumin [g/l]	**43.0** (4.7)	**43.7** (4.4)	**44.4** (4.6)	**44.6** (4.6)	**45.0** (4.4)	**44.5** (5.0)	0.0001

[a] p for difference between means or proportions across alcohol categories.
[b] Numbers given for subsample without missing values for CRP and covariates. Slightly differing numbers in categories for the other dependent variables because of different numbers of missing values. All measures given as arithmetic mean together with standard deviation or proportions except for [c] given as geometric mean with 95% confidence interval. For abbreviations see Table 1.

Table 3 Adjusted[a] means[b] of inflammatory variables in category of daily alcohol intake

Daily alcohol intake [g]	0	>0–20	>20–40	>40–60	>60–80	>80	p^c	p^d
CRP [mg/l]								
Augsburg	**1.46** (1.34–1.58)	**1.29** (1.22–1.35)	**1.31** (1.21–1.43)	**1.40** (1.20–1.63)	**1.32** (1.02–1.69)	**1.32** (0.88–1.99)		
N[e]	*1443*	*1704*	*705*	*362*	*152*	*95*		
Glasgow	**1.49** (1.344–1.65)	**1.32** (1.22–1.43)	**1.46** (1.28–1.68)	**1.46** (1.14–1.87)	**1.70** (1.24–2.34)	**1.52** (1.00–2.34)	0.01	0.003
N[e]	*337*	*549*	*182*	*54*	*33*	*18*		0.046
Lille	**1.69** (1.49–1.92)	**1.34** (1.22–1.47)	**1.28** (1.14–1.44)	**1.58** (1.33–1.87)	**1.65** (1.33–2.03)	**1.87** (1.48–2.36)		
N[e]	*221*	*425*	*239*	*121*	*80*	*67*		
Fibrinogen [g/l]								
Augsburg	**3.03** (2.99–3.08)	**2.89** (2.86–2.92)	**2.77** (2.72–2.82)	**2.76** (2.67–2.86)	**2.75** (2.60–2.89)	**2.74** (2.51–2.97)	0.01	0.12
Glasgow	**2.74** (2.67–2.82)	**2.61** (2.57–2.65)	**2.60** (2.52–2.68)	**2.70** (2.53–2.87)	**2.63** (2.38–2.89)	**2.88** (2.45–3.30)		<0.0001
WBC count [10^9/l]								
Augsburg	**7.21** (7.13–7.29)	**7.12** (7.05–7.19)	**7.06** (6.95–7.17)	**7.09** (6.93–7.25)	**7.26** (7.01–7.51)	**7.45** (7.14–7.76)	0.15	0.08
Lille	**6.54** (6.34–6.73)	**6.41** (6.26–6.55)	**6.38** (6.20–6.57)	**6.59** (6.33–6.86)	**6.71** (6.38–7.04)	**6.55** (6.19–6.91)		0.04
PV [mPa s]								
Augsburg	**1.235** (1.230–1.239)	**1.224** (1.221–1.227)	**1.218** (1.214–1.223)	**1.213** (1.204–1.222)	**1.219** (1.205–1.2233)	**1.223** (1.201–1.245)	0.003	0.009
Glasgow	**1.283** (1.274–1.290)	**1.269** (1.264–1.274)	**1.280** (1.271–1.289)	**1.285** (1.265–1.305)	**1.283** (1.255–1.310)	**1.306** (1.258–1.355)		<0.0001
Albumin [g/l]								
Augsburg	**43.3** (43.0–43.6)	**43.4** (43.2–43.6)	**43.7** (43.3–44.0)	**43.7** (43.0–44.4)	**44.0** (42.9–45.0)	**43.6** (41.9–45.2)	0.07	0.02
Glasgow	**44.5** (43.9–45.0)	**45.0** (44.7–45.3)	**44.8** (44.2–45.4)	**44.7** (43.5–45.9)	**44.6** (42.9–46.4)	**44.0** (40.8–47.1)		0.10

WBC indicates white blood cell count, PV plasma viscosity.

[a] Adjusted for age, sex, body mass index, diabetes, systolic and diastolic blood pressure, smoking status, total cholesterol, education, physical activity, aspirin use, lipid-lowering drugs, history of heart disease.

[b] Geometric mean (95% confidence interval) for CRP, arithmetic mean for all other variables.

[c] *p* for linear term.

[d] *p* for linear and quadratic term for daily alcohol consumption in the pooled sample. Alcohol consumption was used as a continuous variable in these models.

[e] Numbers are given for individuals without missing values for all covariates and CRP. Numbers might differ according to the other inflammatory markers because of slightly differing numbers of missing values.

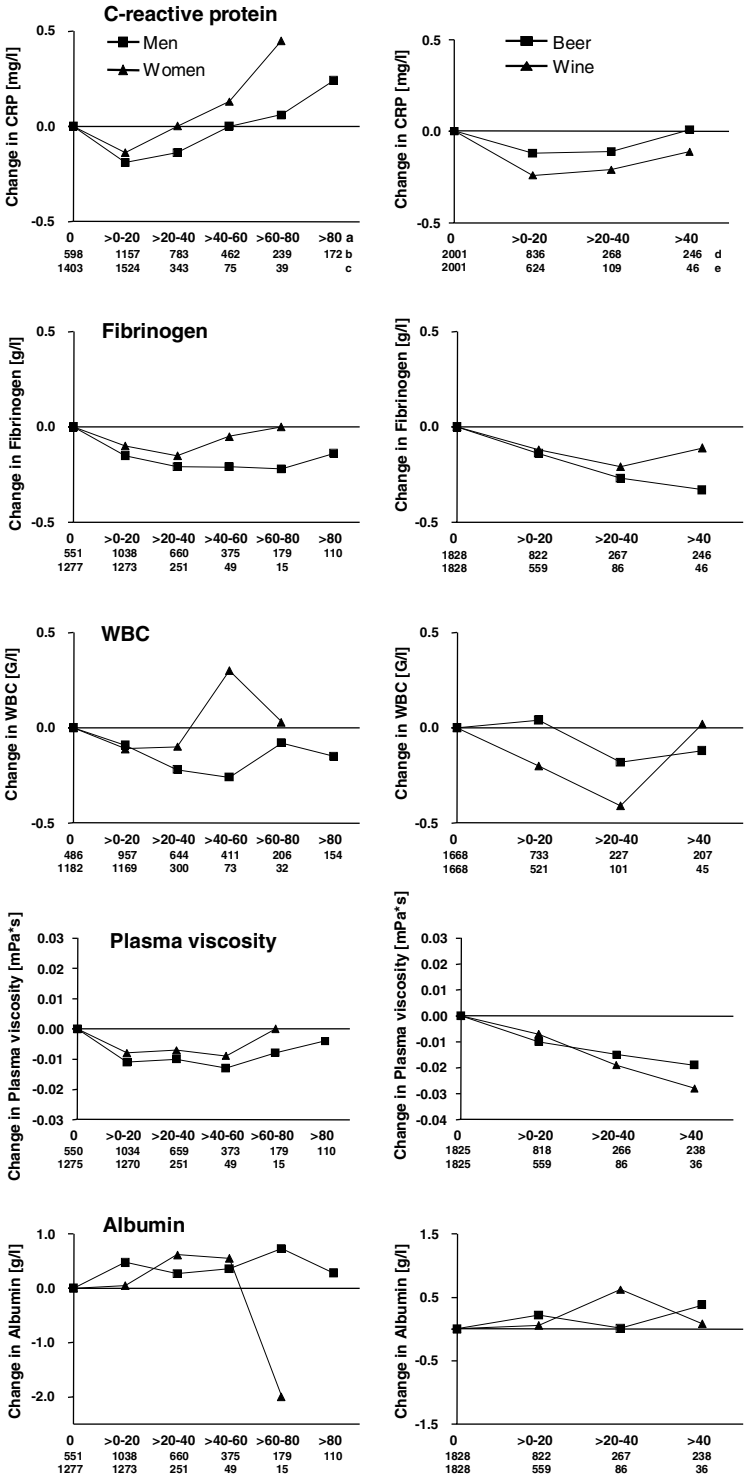

Fig. 1 Differences between adjusted geometric (CRP) or arithmetic (all others) mean concentrations of inflammatory markers in defined categories of alcohol intake in the pooled sample by gender and separately for consumers of either beer and wine exclusively. Throughout, subjects classified as non-drinkers served as reference group. Adjustment for covariates as described in Table 3.

[a]Category of daily alcohol intake.

[b]Numbers of males.

[c]Females.

[d]Exclusive beer consumers.

[e]Wine consumers across categories.

(NF-κB) DNA binding attenuates lipopolysaccharide (LPS) stimulated expression of TNF-α and IL-1β.[29] Inhibition of NF-κB activity was also observed in monocytes from healthy volunteers 3, 6 and 9 h after consumption of moderate amounts of red wine but not after vodka intake.[30] Besides the effects on pro-inflammatory cytokines, alcohol intake favourably affects production of anti-inflammatory cytokines, such as TGF-β and IL-10, both produced by macrophages and T lymphocytes. Alcohol induces production of TGF-β in monocytes and augments TGF-β production in response to bacterial challenge in vitro.[31] Human monocyte IL-10 production is increased after alcohol exposure in vitro.[32] These data suggest that moderate amounts of alcohol may exert anti-inflammatory effects locally in the vascular bed as well as by influencing concentrations of circulating inflammatory mediators as seen in the present study. Furthermore, our findings showing increased concentrations of inflammatory markers with high alcohol intake are in accordance with findings among chronic alcohol abusers. Pro-inflammatory cytokines, such as IL-1, TNF-α, anti-inflammatory cytokines, such as IL-10, chemokines, such as IL-8, and the hepatic acute phase cytokine IL-6, all play a pivotal role in modulating the manifestations of alcoholic liver disease at different stages.[33] TNF-α serum concentrations and those of several other TNF-α inducible cytokines and downstream markers of the acute phase response are increased in patients hospitalised with alcoholic hepatitis and decline during recovery.[34,35] In our pooled sample, those with heavy alcohol intake had higher concentrations of pro-inflammatory markers indicating that the potential beneficial anti-inflammatory effects of moderate alcohol consumption may be reversed by damage in several tissues, including the liver, among heavy drinkers.

Type of beverage and immunomodulation

Some authors have suggested that ingredients of alcoholic beverages other than ethanol might explain the beneficial effects on CHD risk, especially in the case of wine.[36] However, in several studies, a reduced risk of CHD has been reported for moderate consumption of either wine or beer.[37] Moreover, in a case-control study, nested within the physicians' health study, a significant interaction between alcohol consumption, effects on HDL-cholesterol, CHD risk reduction, and a polymorphism in the gene coding for the alcohol dehydrogenase typ 3 (ADH3) were demonstrated, indicating that ethanol itself is mainly responsible for the effect observed.[38] We found lower levels of markers of inflammation among moderate consumers of either wine or beer, even though the effect seen was slightly more pronounced among wine consumers compared to beer drinkers. The small number of those who exclusively consumed spirits did not allow separate analysis of this subgroup. Our results are consistent with those of a recent UK study, which observed similar effects of wine (compared to beer or spirit) consumption on CRP, fibrinogen, viscosity and WBC count among older men.[39]

Limitations

First, several authors have suggested that the relationship between alcohol intake and risk of CAD does not represent a causal relation, but rather reflects a surrogate of healthy life-style and socioeconomic factors.[40] In our study samples, consumers of moderate amounts of alcohol did indeed show more favourable life-style habits compared to subjects in other categories of alcohol intake. In addition, some non-drinkers might have stopped consuming alcohol in the past for health reasons and this study is therefore potentially subject to selection bias. However, results did not change appreciably after adjustment, suggesting that these confounders only partly explain the effects seen. Given that there were a large percentage of missing values in subsamples, a further selection bias cannot be excluded. However, when those who provided complete data were compared to those who did not there was no significant difference in potential confounders. Second, in any observational study like ours, misreporting of alcohol consumption or unknown confounding could be a source of bias. Moreover, assessment of alcohol consumption differed between study samples. However, we adjusted for a large variety of potential confounders, each selected on the basis of known effects and published data. Adjustment for these factors attenuated the effect seen but did not remove it. Third, we did not have further nutrition data to evaluate potential confounding or interaction of nutritional status on the associations studied. Fourth, the observational nature of our study limits causal interference. Fifth, cross-sectional studies do not allow evaluation of time effects. Sixth, pooling data from samples of different origin is afflicted with several potential sources of bias. However, using samples of the MONICA project ensures standardized data collection and high quality. Seventh, all *p*-values need to be interpreted with caution due to the fact that the results from very many significance tests are presented in this paper.

Conclusions and perspectives

We found that non-drinkers and heavy drinkers had higher concentrations of several positive markers and lower levels of a negative biomarker of systemic inflammation than moderate drinkers in representative samples of the general population of three different European countries. These associations are consistent with the hypothesis that an anti-inflammatory action of moderate alcohol intake may represent a link to reduced cardiovascular morbidity and mortality independent of the type of beverage consumed.

Yet some issues remained unresolved and require further research. Experimental studies might help to elucidate the exact mechanisms by which alcohol exerts immunomodulatory effects in the vascular bed. Prospective observational studies are required to assess the dose—response relationship long-term, since interventional endpoint studies are not feasible because of ethical concerns.

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References

1. Corrao G, Rubbiati L, Bagnardi V et al. Alcohol and coronary heart disease: a meta-analysis. *Addiction* 2000;**95**:1505—23.
2. Keil U, Chambless LE, Doring 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—6.
3. Klatzky A. Should patients with heart disease drink alcohol?. *JAMA* 2001;**285**:2004—6.
4. Palmer AJ, Fletcher AE, Bulpitt CJ et al. Alcohol intake and cardiovascular mortality in hypertensive patients: report from the Department of Health Hypertension Care Computing Project. *J Hypertens* 1995;**13**:957—64.
5. Muntwyler J, Hennekens CH, Buring JE et al. Mortality and light to moderate alcohol consumption after myocardial infarction. *Lancet* 1998;**352**:1882—5.
6. 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. *Brit Med J* 1999;**319**:1523—8.
7. Lazarus R, Sparrow D, Weiss ST. Alcohol intake and insulin levels. The normative aging study. *Am J Epidemiol* 1997;**145**:909—16.
8. Libby P. Inflammation in atherosclerosis. *Nature* 2002;**420**:868—74.
9. Danesh J, Collins R, Appleby P et al. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. *JAMA* 1998;**279**: 1477—1482.
10. Koenig W. Fibrin(ogen) in cardiovascular disease: an update. *Thromb Haemost* 2003;**89**:601—9.
11. Koenig W, Sund M, Filipiak B et al. Plasma viscosity and the risk of coronary heart disease: results from the MONICA-Augsburg cohort study, 1984 to 1992. *Arterioscler Thromb Vasc Biol* 1998;**18**:768—72.
12. Djousse L, Rothman KJ, Cupples LA et al. Serum albumin and risk of myocardial infarction and all-cause mortality in the Framingham offspring study. *Circulation* 2002;**106**:2919—24.
13. Nelson S, Kolls JK. Alcohol, host defence and society. *Nat Rev Immunol* 2002;**2**:205—9.
14. Imhof A, Froehlich M, Brenner H et al. Effect of alcohol consumption on systemic markers of inflammation. *Lancet* 2001;**357**:763—7.
15. Albert MA, Glynn RJ, Ridker PM. Alcohol consumption and plasma concentration of C-reactive protein. *Circulation* 2003;**107**:443—7.
16. Stewart SH, Mainous 3rd AG, Gilbert G. Relation between alcohol consumption and C-reactive protein levels in the adult US population. *J Am Board Fam Pract* 2002;**15**:437—42.
17. Nakanishi N, Yoshida H, Okamoto M et al. Association of alcohol consumption with white blood cell count: a study of Japanese male office workers. *J Intern Med* 2003;**253**:367—74.
18. Volpato S, Pahor M, Ferrucci L et al. Relationship of alcohol intake with inflammatory markers and plasminogen activator inhibitor-1 in well-functioning older adults: the health, aging, and body composition study. *Circulation* 2004;**109**:607—12.
19. Sierksma A, Van Der Gaag MS, Kluft C et al. Moderate alcohol consumption reduces plasma C-reactive protein and fibrinogen levels; a randomized, diet-controlled intervention study. *Eur J Clin Nutr* 2002;**56**:1130—6.
20. World Health Organisation. WHO MONICA Project. MONICA Manual CVD/MNC WHO Geneva, 1990.
21. Schaeffler V, Döring A, Winkler G et al. Erhebungen der Alkoholaufnahme: Vergleich verschiedener Methoden. *Ernähr Umsch* 1991;**38**:490—4.
22. Hutchinson WL, Koenig W, Frohlich M et al. Immunoradiometric assay of circulating C-reactive protein: age-related values in the adult general population. *Clin Chem* 2000;**46**:934—8.
23. Harkness J. A new method for the measurement of plasma viscosity. *Lancet* 1963;**2**:280—1.
24. Nelson S, Bagby GJ, Bainton BG et al. The effects of acute and chronic alcoholism on tumor necrosis factor and the inflammatory response. *J Infect Dis* 1989;**160**:422—9.
25. Kolls JK, Xie J, Lei D et al. Differential effects of in vivo ethanol on LPS-induced TNF and nitric oxide production in the lung. *Am J Physiol* 1995;**268**:L991—8.
26. Szabo G, Mandrekar P, Catalano D. Inhibition of superantigen-induced T cell proliferation and monocyte IL-1 beta, TNF-alpha, and IL-6 production by acute ethanol treatment. *J Leukoc Biol* 1995;**58**:342—50.
27. Verma BK, Fogarasi M, Szabo G. Down-regulation of tumor necrosis factor alpha activity by acute ethanol treatment in human peripheral blood monocytes. *J Clin Immunol* 1993;**13**:8—22.
28. Baumann H, Gauldie J. The acute phase response. *Immunol Today* 1994;**15**:74—80.
29. Mandrekar P, Catalano D, Szabo G. Inhibition of lipopolysaccharide-mediated NFkappaB activation by ethanol in human monocytes. *Int Immunol* 1999;**11**:1781—90.
30. Blanco-Colio LM, Valderrama M, Alvarez-Sala LA et al. Red wine intake prevents nuclear factor-kappaB activation in peripheral blood mononuclear cells of healthy volunteers during postprandial lipemia. *Circulation* 2000;**102**:1020—6.
31. Szabo G, Verma BK, Fogarasi M et al. Induction of transforming growth factor-beta and prostaglandin E2 production by ethanol in human monocytes. *J Leukoc Biol* 1992;**52**:602—10.
32. Mandrekar P, Catalano D, Girouard L et al. Human monocyte IL-10 production is increased by acute ethanol treatment. *Cytokine* 1996;**8**:567—77.
33. McClain CJ, Barve S, Deaciuc I et al. Cytokines in alcoholic liver disease. *Semin Liver Dis* 1999;**19**:205—19.
34. Huang YS, Chan CY, Wu JC et al. Serum levels of interleukin-8 in alcoholic liver disease: relationship with disease stage, biochemical parameters and survival. *J Hepatol* 1996;**24**:377—84.
35. Tilg H, Diehl AM. Cytokines in alcoholic and nonalcoholic steatohepatitis. *N Engl J Med* 2000;**343**:1467—76.
36. Bell JR, 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—8.
37. Rimm EB, Stampfer MJ. Wine, beer, and spirits: are they really horses of a different color?. *Circulation* 2002;**105**:2806—7.
38. Hines LM, Stampfer MJ, Ma J et al. Genetic variation in alcohol dehydrogenase and the beneficial effect of moderate alcohol consumption on myocardial infarction. *N Engl J Med* 2001;**344**:549—55.
39. Wannamethee SG, Lowe GD, Shaper G et al. The effects of different alcoholic drinks on lipids, insulin and haemostatic and inflammatory markers in older men. *Thromb Haemost* 2003;**90**:1080—7.
40. Hart CL, Smith GD, Hole DJ et al. Alcohol consumption and mortality from all causes, coronary heart disease, and stroke: results from a prospective cohort study of scottish men with 21 years of follow up. *Brit Med J* 1999;**318**:1725—9.