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ORIGINAL ARTICLE

Relationship between alcohol intake, health and social status and cardiovascular risk factors in the urban Paris-Ile-De-France Cohort: is the cardioprotective action of alcohol a myth?

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Background/Objectives: Observational studies document the inverse relationship between cardiovascular disease (CVD) and moderate alcohol intake. However, the causal role for alcohol in cardioprotection remains uncertain as such protection may be caused by confounders and misclassification. The aim of our study was to evaluate potential confounders, which may contribute to putative cardioprotection by alcohol.
Subjects/Methods: We evaluated clinical and biological characteristics, including cardiovascular (CV) risk factors and health status, of 149 773 subjects undergoing examination at our Center for CVD Prevention (The Urban Paris-Ile-de-France Cohort). The subjects were divided into four groups according to alcohol consumption: never, low ($\leqslant$10 g/day), moderate (10–30 g/day) and high ($>$30 g/day); former drinkers were analyzed as a separate group.
Results: After adjustment for age, moderate male drinkers were more likely to display clinical and biological characteristics associated with lower CV risk, including low body mass index, heart rate, pulse pressure, fasting triglycerides, fasting glucose, stress and depression scores together with superior subjective health status, respiratory function, social status and physical activity. Moderate female drinkers equally displayed low waist circumference, blood pressure and fasting triglycerides and low-density lipoprotein-cholesterol. Alcohol intake was strongly associated with plasma high-density lipoprotein-cholesterol in both sexes. Multivariate analysis confirmed that moderate and low drinkers displayed better health status than did never drinkers. Importantly, few factors were causally related to alcohol intake.
Conclusions: Moderate alcohol drinkers display a more favorable clinical and biological profile, consistent with lower CV risk as compared with nondrinkers and heavy drinkers. Therefore, moderate alcohol consumption may represent a marker of higher social level, superior health status and lower CV risk.
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Keywords: alcohol; HDL-C; cardiovascular risk factors; epidemiology

Introduction

An inverse association between moderate alcohol consumption and cardiovascular disease (CVD) has been established in prospective observational epidemiological studies in several countries. Meta-analyses (Maclure, 1993; Cleophas, 1999; Corrao *et al*., 2000; Di Castelnuovo *et al*., 2002, 2006) have confirmed that self-reported consumption of one (~10 g alcohol) to three (~30 g alcohol) standard alcoholic drinks per day is associated with a 20–25% reduction in the risk of CVD. The lower risk of CVD observed in moderate drinkers is often attributed to the beneficial effects of alcohol on plasma lipids and lipoproteins (Chapman, 2006). Other potential explanations include the effect of alcohol on hemostatic factors (Rimm *et al*., 1999) and of antioxidants present in

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red wine (Leikert *et al*., 2002). Taken together, these data have been translated into the message that 'small-to-moderate amounts of alcohol are good for your health'. This message is of particular importance in France where the mean alcohol intake per inhabitant is one of the highest in the world.

However, findings in observational studies should be viewed with caution because the number of bias may not always be taken into account. A growing body of evidence suggests that the apparent protection afforded by alcohol intake against CVD might be due in part to misclassification and confounding (Shaper *et al*., 1988; Tjonneland *et al*., 1999; Mortensen *et al*., 2001; Naimi *et al*., 2005; Fillmore *et al*., 2007, 2008; Stockwell *et al*., 2007). To evaluate these confounding, we undertook a large population study to analyze the relationship between alcohol intake and other cardiovascular (CV) risk factors in a large French population. We assessed a number of key factors not taken into account in earlier well-conducted studies; these include social factors, health status (mental well-being, subjective health status), respiratory function, anthropometric values, heart rate and pulse pressure (PP).

Materials and methods

Subjects were examined at the IPC (Clinical and Preventive Investigation Center in Paris, France). This medical center, which is subsidized by the French National Health Care system (Social Security-CNAMTS), offers a complementary medical examination to all working and retired individuals, as well as their families once every 5 years. It is one of the largest medical centers of this kind in France, carrying out ~25 000 health examinations per year for people living in the Paris area.

Our study population underwent a health checkup at the IPC Center between January 1999 and December 2005 and was composed of 149 773 subjects (97 406 men and 52 367 women) with a mean age of 47.6 ± 15 and 47.0 ± 12 years, respectively).

Supine blood pressure (BP) was measured in the right arm using a manual mercury sphygmomanometer, after a 10-min resting period. The first and the fifth Korotkoff phases were used to define systolic BP (SBP) and diastolic BP (DBP), respectively. The mean of three measurements was considered as the BP value. PP was defined as the difference between SBP and DBP. Waist circumference (WC) was measured using an inelastic tape placed midway between the lower ribs and iliac crests on the mid-axillary line. Standard biological parameters (enzymatic method, automat HITACHI 917 (Roche, Meylan, France); colorimetric method for albumin dosage and hematology: ABX, Pentra 120, Meylan, France) were measured under fasting conditions; high-density lipoprotein-cholesterol (HDL-C) was measured by direct enzymatic assay with cyclodextrin (Roche Diagnostics, Basel, Switzerland). A resting electrocardiogram was recorded. Respiratory function was assessed by spirometry by measuring forced expiratory volume (FEV1). Tobacco consumption (never smoker, ex-smoker and current smoker), physical activity (regular physical activity: yes or no), personal medical history, current medications and alcohol consumption, social status and occupational activity were assessed using a self-administered questionnaire. Stress and depression scores were assessed by validated questionnaires (Beck *et al*., 1974; Cohen *et al*., 1983); Subjected Health Status (SHS) scores were collected with a self-estimation on a scale between 0 and 10. Alcohol intake was quantified as the number of standardized glasses of alcohol (10 g per glass) consumed per day. Each type of alcoholic beverage (such as cider and beer, wine, appetizer) was recorded. Total alcohol intake was calculated as the sum of all types of alcohol consumed and the corresponding quantity (as grams of alcohol) was estimated. All clinical and biological parameters were evaluated on the same day of the examination.

The IPC Center received authorization from the National Committee of Information and Civil Liberty to conduct these analyses. All subjects gave their informed consent at the time of the examination.

Statistical analysis

Alcohol consumption was divided into five classes : (1) no alcohol consumption, (2) low alcohol consumption (less than one glass per day), (3) moderate alcohol consumption (between one and three glasses per day), (4) high alcohol consumption (more than three glasses) and (5) subjects who previously consumed alcohol but who no longer did (former drinkers). As a consequence of the heterogeneity in the group of former drinkers (time elapsed since cessation of alcohol consumption, reason for this cessation, etc.), data in this group were analyzed separately.

For quantitative variables, the four first groups were compared by multivariate model analysis, which included age to take into account the difference in age observed between the different groups; respiratory function (FEV1) was compared across the groups before and after further adjustment for tobacco status. For qualitative variables, comparisons were made using the χ^2 test. As one may hypothesize that the relationships between alcohol and health and social status are not identical in males and females, we analyzed these relationships on the basis of stratification by gender. All parameters associated with alcohol consumption in univariate analysis were included in a multivariate model. Forward regression analysis was carried out and all variables remaining in the model were significant with $P<0.05$. All statistical analyses were performed using the SAS statistical software (version 8.02; SAS Institute, Cary, NC, USA).

Results

Data collected from a total of 149 773 subjects (97 406 men and 52 367 women) were analyzed. The average ages of men

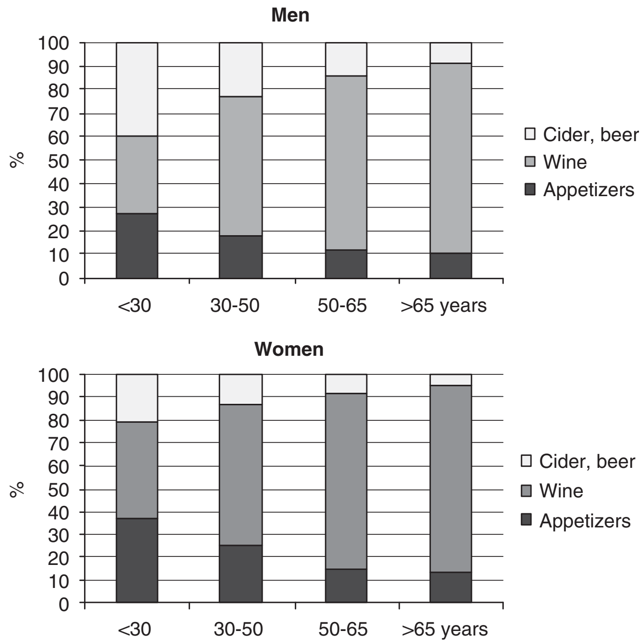

Figure 1 Nature of the preferred alcoholic beverage according to sex and age.

and women were 47.6 ± 15 and 47.0 ± 12 years, respectively. In this population, 13.7% of men and 23.9% of women were abstinent (4.5% former drinkers and 9.2% never drinkers in men; 20.1% never drinkers and 3.1% former drinkers in women). Total alcohol intake increased with age both in men and in women. Figure 1 presents the type of alcoholic beverage preferred according to sex and age. With the exception of the subgroup of young subjects (<30 years of age), alcoholic beverages mainly consisted of wine. In addition, wine consumption increased with age, whereas those of beer and appetizers decreased ($P<0.0001$).

Age-adjusted clinical characteristics of the study population according to alcohol consumption (never, low, moderate and heavy drinkers) are presented in Table 1 for men and in Table 2 for women. In women, body mass index (BMI), WC, hip circumference, waist-to-hip ratio and the prevalence of obesity (BMI $>30\,kg/m^2$) were all lowest in moderate drinkers and highest in never drinkers. No clear relationship was observed between alcohol consumption and anthropometric variables in men; however, moderate drinkers were less likely to be obese as compared with other groups. In women, SBP and DBP differed as a function of alcohol consumption, being lowest in moderate drinkers and highest in never drinkers. Moreover, in women, PP was negatively associated with alcohol intake, being highest in female never drinkers. In men, the lowest value for SBP was observed in low drinkers, whereas there was a progressive increase in DBP with increase in alcohol intake; PP was the lowest in low and moderate drinkers as compared with never drinkers. Heart rate was the lowest in moderate drinkers in both men and women.

There was a significant positive relationship between smoking and alcohol consumption. In women, moderate drinkers were more likely to declare that they practiced regular physical activity as compared with the other groups. By contrast in men, never drinkers reported the highest level of physical activity. In both genders, respiratory function assess by FEV1 was highest in moderate drinkers and lowest in never drinkers. Similar results were observed after adjustment for tobacco consumption (data not shown). In men, the percentage of subjects living alone was the highest among never drinkers and lowest among moderate drinkers. By contrast, in women, moderate drinkers were more likely to live alone than never drinkers. The SHS across the groups is presented in Figure 2. The proportion of subjects with a low evaluation of their SHS score was lowest in the group of moderate alcohol consumers and the highest in never drinkers; this finding was observed in both genders. Score values of depression and stress differed significantly among groups distinguished by the level of alcohol consumption. For both scores, minimal values were observed among moderate alcohol consumers in both women and men. Higher values of these scores were observed among individuals who were abstainers. Intermediate values were observed among heavy drinkers.

Tables 3 and 4 show age-adjusted means of biological parameters in men and women, respectively. Mean globular volume and GGT (γ-glutamyl transpeptidase) were positively associated with self-reported alcohol consumption, thereby confirming the validity of data collection regarding alcohol intake. In both genders, total cholesterol levels were positively associated with alcohol consumption. The lowest levels of total cholesterol were observed among never drinkers, whereas the highest were observed among heavy drinkers. In men, low-density lipoprotein-cholesterol levels were also positively associated with alcohol consumption. In women, the lowest values of low-density lipoprotein-cholesterol were observed among moderate drinkers. In both genders, the lowest values of plasma triglycerides and fasting blood glucose were observed among low or moderate drinkers.

Mean values (s.e.m.) of HDL-C concentration are presented in Tables 3 and 4 (for men and women, respectively) and in Figure 3. In both genders, the level of HDL-C was the lowest among never drinkers and increased linearly with alcohol consumption. This relationship was similar across age groups, and equally persisted in hypertriglyceridemic subjects. Moreover, this relationship was independent of the type of alcoholic beverage consumed (data not shown). A multivariate analysis was performed to determine the factors associated with low or moderate alcohol consumption (Table 5). This analysis revealed that FEV1, age, current smoking, HDL-C, general health status, a lower anxiety score, cholesterol, GGT, a lower heart rate, the absence of diabetes and an absence of regular physical activity were the major factors, which were positively associated with low or moderate alcohol consumption.

Table 1 Age-adjusted clinical characteristics of men in the urban Paris-Ile-de- France Cohort

	Alcohol intake				
	Never	*Low*	*Moderate*	*Heavy*	P *for trend*
N (%)	8921 (9.2)	46 550 (47.8)	24 221 (24.9)	13 311 (13.7)	
Age (years)	42.8 (14.0)	45.4 (12.1)	49.4 (12.0)	51.1 (11.3)	<0.0001
Weight (kg)	75.6 (0.13)	77.7 (0.06)	77.3 (0.08)	78.3 (0.10)	<0.0001
BMI (kg/m^2)	25.4 (0.04)	25.5 (0.02)	25.3 (0.02)	25.6 (0.03)	<0.0001
% Obesity (*n*)[a]	11.6 (1026)	10.1 (4705)	9.2 (2214)	12.3 (1628	<0.0001
WC (cm)	88.4 (0.10)	89.4 (0.05)	89.4 (0.06)	90.1 (0.09)	<0.0001
Hip circumference (cm)	99.3 (0.08)	100.1 (0.04)	99.9 (0.05)	99.7 (0.07)	<0.0001
WHR	0.89 (0.0007)	0.89 (0.0002)	0.89 (0.0004)	0.90 (0.001)	<0.0001
SBP (mm Hg)	133.8 (0.18)	133.1 (0.08)	133.4 (0.11)	136.1 (0.15)	<0.0001
DBP (mm Hg)	78.8 (0.12)	79.3 (0.05)	79.7 (0.07)	81.6 (0.10)	<0.0001
PP (mm Hg)	54.9 (0.12)	53.7 (0.05)	53.7 (0.07)	54.4 (0.10)	<0.0001
HR (beats per minute)	63.6 (0.11)	62.0 (0.05)	62.0 (0.07)	63.5 (0.09)	<0.0001
FEV1	0.86 (0.002)	0.93 (0.0008)	0.94 (0.001)	0.91 (0.001)	<0.0001
% Current smokers (*n*)	8.6 (1656)	29.4 (13 664)	31.9 (7722)	44.9 (5981)	<0.0001
Anxiety score[b]	4.48 (0.03)	3.45 (0.01)	3.45 (0.02)	3.92 (0.03)	<0.0001
Depression score[c]	1.35 (0.02)	1.23 (0.01)	1.25 (0.02)	1.69 (0.02)	<0.0001
SHS score[d]	20.2 (1798)	12.0 (5570)	12.0 (2906)	17.2 (2285)	<0.0001
% Physical activity (yes) (*n*)	49.0 (4367)	47.2 (21 970)	48.1 (11 641)	47.0 (6249)	<0.05
% Hypertensives (*n*)	29.9 (2560)	32.4 (14 418)	38.2 (8964)	46.8 (5699)	<0.0001
% Diabetics (*n*)	4.7 (416)	2.8 (1236)	3.1 (742)	4.6 (568)	<0.0001
% Subjects living alone (*n*)	29.4 (2608)	21.9 (10 195)	18.8 (4548)	23.9 (3172)	<0.0001
Education (%, n)					
No educational or professional diploma	17.4 (1151)	6.3 (2119)	6.3 (782)	10.3 (902)	<0.0001
High school diploma, or superior	21.0 (1390)	39.0 (13 040)	42.9 (5327)	34.6 (3019)	<0.0001
SPC (%, n)					
Unemployed	28.1 (2452)	12.5 (5617)	9.9 (2357)	16.0 (1985)	
Profession, white collar	18.6 (1626)	49.2 (22 170)	56.5 (13 409)	48.2 (5978)	<0.0001
Employees, blue collar	53.3 (4660)	38.3 (17 261)	33.6 (7978)	35.8 (4430)	

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; FEV1, forced expiratory volume in 1 s; HR, heart rate; PP, pulse pressure; SBP, systolic blood pressure; SHS, subjective health status; SPC, socio-professional category; VC, vital capacity; WC, waist circumference; WHR, waist-to-hip ratio.
Values are (means (s.e.m.)).
[a]BMI >30 kg/m^2.
[b](Cohen *et al*., 1983).
[c](Beck *et al*., 1974).
[d]% (*n*) of subjects with a less favorable SHS (score ⩽5/10).

Discussion

In this cross-sectional study, alcohol consumption was strongly associated with several clinical, social and biological characteristics that favor a superior overall health status and a lower risk of CVD in moderate alcohol drinkers as compared with never drinkers. Our multivariate analysis, which included all factors associated with alcohol consumption in the univariate analysis, confirmed that moderate and low drinkers display a superior health status as compared with never drinkers. Importantly, few of these factors seem causally related to alcohol consumption.

In this study, the relationship between alcohol intake and HDL-C levels was strong and constant in both sexes. Moreover, it was independent of the type of alcoholic beverage consumed. In this context, it is relevant that Rimm *et al*. (1999) quantified the effect of alcohol consumption in a meta-analysis of 25 studies, and clearly established a causal relationship between alcohol and HDL-C levels. However, to our knowledge, the causal relationship between alcohol-related increase in HDL-C levels and reduction in CV risk remains to be established. Previous studies have focused on the importance of HDL functionality, that is, the capacity of HDL particles to protect against atherosclerosis, which might be more informative than quantitative data on HDL-C (Kontush and Chapman, 2006). Alcohol may impact HDL metabolism and functionality, but there are few data that show that this effect is beneficial. Some studies have suggested that ethanol may impair HDL function despite an increase in HDL-C (Hannuksela *et al*., 1992; Marmillot *et al*., 2007). Thus, the influence of alcohol on HDL cannot simply be interpreted as a cardioprotective effect.

In our study, the BMI and percentage of obese subjects in both men and women, as well as the WC in women, were lowest in moderate drinkers. The earliest observational studies reported discordant results regarding the association between alcohol intake and anthropometric variables (Suter, 2005). Several studies reported a J-shaped relationship between

Table 2 Age-adjusted clinical characteristics of women in the urban Paris-Ile-de- France Cohort

	Alcohol intake				
	Never	*Low*	*Moderate*	*Heavy*	P-*value*
N (%)	10 523 (20.1)	30 547 (58.4)	7705 (14.7)	1581 (3.0)	
Age (years)	43.1 (15.9)	47.6 (14.4)	53.4 (14.0)	51.5 (13.3)	<0.0001
Weight (kg)	64.3 (0.12)	62.0 (0.07)	60.9 (0.14)	62.3 (0.30)	<0.0001
BMI (kg/m^2)	25.4 (0.04)	23.9 (0.03)	23.2 (0.05)	23.5 (0.11)	<0.0001
% Obesity (*n*)[a]	17.5 (1825)	9.0 (2746)	6.7 (512)	8.1 (128)	<0.0001
WC (cm)	79.4 (0.10)	76.0 (0.06)	75.2 (0.12)	76.5 (0.27)	<0.0001
Hip circumference (cm)	99.3 (0.09)	97.1 (0.05)	96.1 (0.11)	96.5 (0.23)	<0.0001
WHR	0.80 (0.0006)	0.78 (0.0004)	0.78 (0.001)	0.79 (0.002)	<0.0001
SBP (mm Hg)	130.5 (0.18)	127.7 (0.10)	127.3 (0.21)	128.6 (0.46)	<0.0001
DBP (mm Hg)	76.3 (0.11)	75.2 (0.06)	75.1 (0.13)	76.6 (0.28)	<0.0001
PP (mm Hg)	54.3 (0.12)	52.5 (0.07)	52.3 (0.14)	52.0 (0.32)	<0.0001
HR (beats per minute)	66.7 (0.10)	64.3 (0.06)	64.0 (0.12)	64.5 (0.26)	<0.0001
FEV1	0.90 (0.002)	0.93 (0.001)	0.94 (0.002)	0.91 (0.004)	<0.0001
% Current smokers (*n*)	13.5 (1419)	24.8 (7575)	28.0 (2163)	46.2 (731)	<0.0001
Anxiety score[b]	5.33 (0.03)	4.59 (0.02)	4.61 (0.04)	5.10 (0.08)	<0.0001
Depression score[c]	2.70 (0.03)	2.26 (0.02)	2.33 (0.04)	2.99 (0.08)	<0.0001
SHS score[d]	32.0 (3359)	19.5 (5937)	18.2 (324)	22.9 (361)	<0.0001
% Hypertensives (*n*)	27.2 (2743)	27.7 (8193)	34.2 (2513)	35.4 (506)	<0.0001
% Diabetics (*n*)	3.7 (378)	1.52 (457)	1.76 (131)	2.19 (32)	<0.0001
% Subjects living alone (*n*)	29.5 (3100)	35.7 (10 891)	33.5 (2579)	38.0 (600)	<0.0001
Education (%,n)					
No educational or professional diploma	17.6 (1379)	7.6 (1531)	6.4 (263)	6.4 (74)	<0.0001
High school diploma, or superior	15.3 (1200)	27.4 (5525)	29.8 (1219)	33.7 (390)	<0.0001
SPC (%,n)					
Unemployed	43.4 (4474)	23.7 (7147)	24.5 (1832)	31.2 (456)	
Profession, white collar	9.4 (974)	23.7 (7128)	28.6 (2138)	30.5 (445)	<0.0001
Employees, blue collar	47.2 (4873)	52.6 (15 842)	46.9 (3501)	38.3 (558)	

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; FEV1, forced expiratory volume in 1 s; HR, heart rate; PP, pulse pressure; SBP, systolic blood pressure; SHS, subjective health status; SPC, socio-professional category; VC, vital capacity; WC, waist circumference; WHR, waist-to-hip ratio.
Values are (means (s.e.m.)).
[a]BMI $>30\,kg/m^2$.
[b](Cohen *et al*., 1983).
[c](Beck *et al*., 1974).
[d]% (*n*) of subjects with a less favorable SHS (score $\leqslant 5/10$).

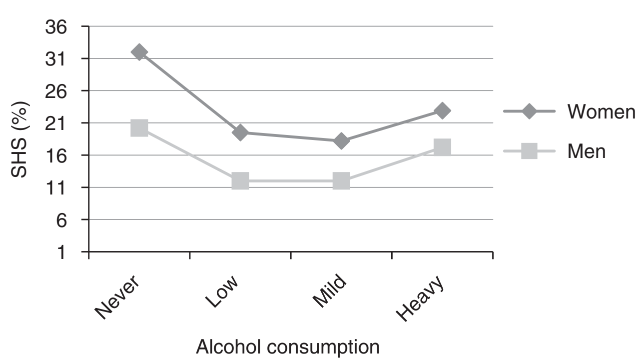

Figure 2 Percentage (%) of subjects with a less favorable SHS (score $\leqslant 5$) as a function of alcohol intake in both women and men. SHS, Subjective Health Status.

alcohol consumption and BMI and waist-to-hip ratio, such that light-to-moderate drinking was believed to exert beneficial effects in reducing weight, whereas nondrinking and heavy or risky drinking exerted the opposite effect (Colditz *et al*., 1991; Lukasiewicz *et al*., 2005; Arif and Rohrer, 2005). Other studies have shown a positive relationship between alcohol intake and BMI and/or WC. Thus, there is no clear evidence of a favorable or an unfavorable effect of alcohol intake on weight and body fat distribution. Lower WC noncausally related to moderate alcohol intake might thus, in part, account for the apparent protective effect of alcohol intake.

In both the sexes SBP and DBP was lower in moderate drinkers as compared with abstainers. Moreover, PP, which might represent a potent CV risk factor (Panagiotakos *et al*., 2005), was significantly lower in drinkers. These results are strongly suggestive of a confounding effect. Indeed, moderate alcohol consumption is known to have no effect or even to increase BP (Suter, 2005).

Importantly, social status was strikingly different across the groups. Our findings show that moderate alcohol consumption is a powerful general indicator of optimal social status. These findings are concordant with those of other published reports. Thus, Mortensen *et al*. (2001) concluded that the association between drinking habits

Table 3 Age-adjusted biological characteristics of men in the urban Paris-Ile-de- France Cohort

	Alcohol intake				
	Never	*Low*	*Moderate*	*Heavy*	P-*value*
N (%)	8921 (9.2%)	4655 (47.8%)	24 221 (24.9%)	13 311 (13.7%)	
TC (mg/dl)	200 (0.004)	214 (0.002)	217 (0.003)	222 (0.003)	<0.0001
FBG (mg/dl)	99 (0.002)	98 (0.001)	98 (0.001)	100 (0.002)	<0.0001
Triglycerides (mg/dl)	109 (0.008)	111 (0.004)	110 (0.005)	122 (0.007)	<0.0001
HDL-C (mg/dl)	52.2 (0.15)	55.9 (0.07)	58.2 (0.09)	60.1 (0.12)	<0.0001
LDL-C (mg/dl)	126.8 (0.38)	135.8 (0.17)	137.4 (0.23)	138.1 (0.31)	<0.0001
MGV (μ3)	89.2 (0.09)	90.9 (0.04)	92.3 (0.05)	93.8 (0.08)	<0.0001
Gamma-GT (IU/l)	30.0 (0.59)	34.5 (0.26)	38.7 (0.36)	58.9 (0.48)	<0.0001

Abbreviations: ANCOVA, analysis of covariance; FBG, fasting blood glucose; gamma-GT, gamma-glutamyl transpeptidase; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; MGV, mean globular volume; P, difference between groups by ANCOVA; TC, total cholesterol.
Values are (means (s.e.m.)).

Table 4 Age-adjusted biological characteristics of women in the urban Paris-Ile-de- France Cohort

	Alcohol intake				
	Never	*Low*	*Moderate*	*Heavy*	P-*value*
N (%)	10 523 (20.1%)	30 547 (58.4%)	7705 (14.7%)	1581 (3.0%)	
Cholesterol (mg/dl)	206 (0.004)	212 (0.004)	212 (0.004)	216 (0.01)	<0.0001
FBG (mg/dl)	94 (0.01)	92 (0.001)	93 (0.002)	94 (0.004)	<0.0001
Triglycerides (mg/dl)	90 (0.004)	82 (0.003)	81 (0.005)	90 (0.01)	<0.0001
HDL-C (mg/dl)	64.0 (0.16)	70.1 (0.10)	73.1 (0.2)	75.1 (0.4)	<0.0001
LDL-C (mg/dl)	124.6 (0.33)	125.2 (0.19)	122.8 (0.38)	123.1 (0.84)	<0.0001
MGV (μ3)	88.8 (0.10)	90.9 (0.06)	92.5 (0.11)	94.1 (0.27)	<0.0001
Gamma-GT (IU/l)	21.7 (0.3)	21.1 (0.2)	24.6 (0.4)	38.4 (0.9)	<0.0001

Abbreviations: ANCOVA, analysis of covariance; FBG, fasting blood glucose; gamma-GT, gamma-glutamyl transpeptidase; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; MGV, mean globular volume; P, difference between groups by ANCOVA.
Values are (means (s.e.m.)).

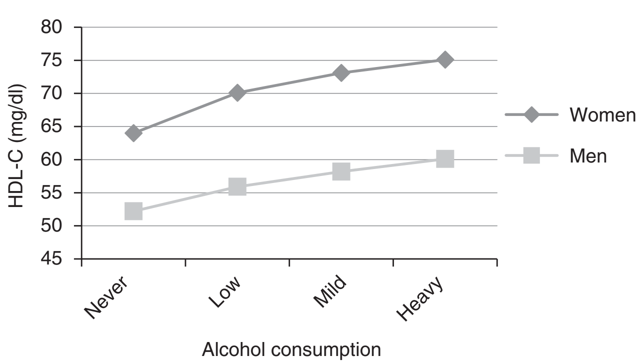

Figure 3 Mean plasma HDL-C concentration expressed as a function of the level of alcohol intake in both women and men.

and social and psychological characteristics in Denmark may in a large part explain the apparent health benefits of wine. Another study conducted by Naimi *et al*. (2005) led to a similar conclusion in a population-based telephone survey of US adults. The majority of well-conducted studies which have assessed CVD as a function of alcohol intake do not take into account adjustment for social status. Residual confounding is likely when a single index of social status is used as a covariate in other studies of the beneficial CV effect of alcohol.

Table 5 Multivariate analysis of determinants of moderate or low alcohol consumption vs never consumption

Variable	*Score* χ^2	*OR*	*CI*
High vs low socio-professional status	3069.7	0.571	0.551–0.592
FEV1	953.8	1.007	1.006–1.008
Age	1506.3	1.038	1.036–1.041
Current smoker (Y/N)	1044.2	2.86	2.69–3.04
HDL-C (mg/dl)	827.5	1.021	1.019–1.022
Good Health Evaluation (SHS<5)	323.3	1.533	1.446–1.626
Cholesterol (mg/dl)	164.6	1.003	1.002–1.004
Gamma-GT	114.8	1.009	1.007–1.010
Anxiety score	112.6	0.957	0.950–0.965
HR	81.8	0.989	0.986–0.991
Diabetes (Y/N)	22.2	0.716	0.622–0.825
Waist circumference (cm)	27.11	0.990	0.987–0.994
Gender (M/F)	12.0	1.13	1.06–1.21
Hypertension (Y/N)	5.1	1.07	1.009–1.131

Abbreviations: CI, confidence interval; FEV1, forced expiratory volume in 1 s; gamma-GT, gamma-glutamyl transpeptidase; HDL-C, high-density lipoprotein-cholesterol; HR, heart rate; OR, odds ratio; SHS, subjective health status. All parameters associated with alcohol consumption in univariate analysis were included in the multivariate model. Forward regression analysis was carried out and all variables remaining in the model were significant with $P<0.05$.

Global health status assessed by a scale of SHS was highest in moderate drinkers. Subjective health provides a global assessment of health status and is a strong predictor of total mortality (Idler and Benyamini, 1997). Our present findings are consistent with those of the study by Stranges *et al*. (2006) in which noncurrent drinkers reported poorer physical and mental health than did life-time abstainers and current drinkers. A similar pattern was observed for the relationship between depression score, anxiety score and alcohol intake. No evidence was obtained to support the conclusion that this relationship might be causal in nature.

Our data collection included measurement of respiratory function. Drinkers displayed higher FEV1 in 1 s and forced vital capacity. Impaired pulmonary function is a strong predictor of CV and all-cause mortality in the general population independent of smoking (Friedman *et al*., 1976; Schunemann *et al*., 2000). Thus, our findings may partially explain the apparent protective effect of alcohol. Whether the relationship between alcohol intake and pulmonary function is causal remains indeterminate as published literature shows conflicting results. (Cohen *et al*., 1980; Lebowitz, 1981; Sparrow *et al*., 1983; Lange *et al*., 1988; Zureik *et al*., 1996; Murray *et al*., 1998; Twisk *et al*., 1998). Therefore, our findings support the need to integrate pulmonary function in multivariate analysis when studying the effect of alcohol on CVD or health status.

Our data thus show that several social, clinical and biological variables differ markedly according to alcohol consumption. Other studies are consistent with our data and show that moderate drinkers, particularly wine drinkers, consume a healthy diet and have a healthy behavioral pattern as compared with other drinkers or abstainers (Tjonneland *et al*., 1999; Ruidavets *et al*., 2004).

Our multivariate analysis showed that several risk factors which are rarely or never taken into account in previous observational studies are associated with alcohol intake independently of traditional risk factors. Interestingly, FEV1, socio-professional status, SHS, anxiety score, WC and heart rate all remained associated with alcohol consumption with a more favorable profile in low or moderate drinkers vs never drinkers. These results emphasize the caution with which one must interpret the results of observational studies. Another concern in observational studies is misclassification. Shaper *et al*. (1988) proposed that ex-drinkers who ceased drinking because of illness or CV risk factors were often misclassified with never drinkers, thus artifactually increasing the CV risk of abstainers. This hypothesis was discarded in some studies, which reported association after exclusion of ex-drinkers (Fagrell *et al*., 1999). However, in two meta-analyses (Fillmore *et al*., 2007; Stockwell *et al*., 2007), the apparent protective effect of alcohol disappeared when occasional and ex-drinkers were excluded from the group of abstainers subjects.

Taken together, our results raise the possibility that the protective effect of alcohol may be an artifactual association due to uncontrolled confounding. Although several observational studies on alcohol consumption were of very high quality, bias cannot be excluded. As emphasized by previous examples with hormonal replacement therapy or antioxidant supplementation (Neuzil *et al*., 2001), the observational design cannot lead to conclude to causal relationships. However, our results cannot eliminate the cardioprotective effect of alcohol.

The strength of this report emanates from the use of a relatively healthy large cohort of subjects who were characterized with standardized and validated clinical and biological methods. The main weakness of our study is its cross-sectional design. Another potential limitation concerns the fact that alcohol intake was based on self-reported data with the possibility of misclassification of exposure. However all previous studies have assessed alcohol intake in a similar manner. The positive relationship observed between plasma levels of GGT, MCV and the ordered groups of alcohol consumption led us to conclude that classification on the basis of the quantity of alcohol consumed was satisfactory. Furthermore, misclassification would have reduced the relationship between alcohol intake and risk factors. The third limitation in our study involved the self-selection of subjects who attended the screening centers. However, analysis of the comorbidity and causes of mortality of subjects in our cohort lead us to consider this population as representative of the population of the urban region of Paris-Ile-de -France.

In conclusion, our data show that mild and moderate drinkers display a more favorable health status and a lower CV risk profile (especially when we consider nontraditional CV risk factors) than never drinkers and heavy drinkers. No human clinical data other than those from observational studies are currently available to support a causal relationship between alcohol intake and CVD. Rather than a beneficial effect of alcohol consumption on classic or emerging CV risk factors, we must hypothesize that moderate drinking is a marker of a higher social level, superior general health status and lower CV risk. Future epidemiological studies assessing the relationship between alcohol and CVD should cautiously select the covariates for the multivariate analysis. Our data suggest that it is clearly premature to promote alcohol consumption as the basis of CV protection until such time as the causal role of alcohol in cardioprotection is fully proven.

Conflict of interest

The authors declare no conflict of interest.

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