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ABSTRACT

Background and aims: To estimate the association between patterns of alcohol consumption and biomarkers of coronary heart disease (CHD) risk.

Methods and Results: Cross-sectional study among 10,793 individuals representative of the Spanish population aged ≥18 years. The threshold between moderate and heavy drinking was 40 g of alcohol/day in men and 24 g/day in women. Binge drinking was defined as intake of ≥80 g of alcohol in men and ≥60 g in women at any drinking occasion in the preceding 30 days. Analyses were performed with generalized linear models with adjustment for the main confounders, and results were expressed as the percentage change in the geometric mean (PCGM). Compared to non-drinkers, moderate and heavy drinkers had progressively higher serum HDL-cholesterol, with a PCGM ranging from 4.8% (95% CI: 3.7 to 6.0%) in moderate drinkers without binge drinking (MNB) to 9.6% (5.1 to 14.2%) in heavy drinkers with binge drinking (HB). Fibrinogen decreased progressively with alcohol intake, from -2.2% (-3.1 to -1.3%) in MNB to -5.8% (-9.4 to -2.0%) in HB. Leptin, glycated hemoglobin and the HOMA-index also decreased with increasing alcohol intake, and particularly with binge drinking.

Conclusions: Moderate alcohol intake is associated with improved HDL-cholesterol, fibrinogen and markers of glucose metabolism, which is consistent with the reduced CHD risk of moderate drinkers in many studies. Heavy and binge drinking were also associated with favorable levels of CHD biomarkers; since these drinking patterns produce substantial health harms, our results should not be used to promote alcohol consumption.

Keywords: Alcohol; drinking patterns; biomarkers; coronary heart disease

Introduction

The effect of alcohol on the risk of coronary heart disease (CHD) depends on the drinking pattern[1]. In many prospective studies the intake of small to medium amounts of alcohol has been consistently associated with a lower risk of CHD[2]. Indirect support of a causal protective effect of moderate alcohol intake on CHD derives from short-term trials showing an improvement in CHD biomarkers, in particular an elevation of HDL-cholesterol and a reduction of fibrinogen[3].

The effects of heavy drinking on CHD are more uncertain. The effect of regular heavy drinking (>60 g alcohol/day) is insufficiently known because it is relatively infrequent in most populations and is disproportionately missed in usual cohort studies[1]. As regards irregular heavy drinking, it has been associated with a 45% increase in CHD risk after adjustment for the volume of alcohol consumed; thus, it seems that any cardioprotective effect of moderate alcohol consumption may be negated by irregular heavy drinking occasions[4]. The mechanisms of the cardiovascular effect of heavy drinking are poorly understood; while a few clinical trials suggest that heavy drinking increases HDL-cholesterol[5-7], it may also exert a detrimental effect on thrombosis, blood pressure and atrial fibrillation[8-9].

Short-term trials may not be appropriate to characterize the effect of long-term drinking patterns. Moreover, the effect of each type of beverage on biomarkers of CHD risk has not been well established, because most studies used wine as the alcohol intervention[3]. Therefore, the characterization of the impact of habitual drinking patterns requires information from population-based studies. Unfortunately, most observational studies have focused on regular moderate alcohol consumption, so information on the association between the main drinking patterns, including heavy and binge drinking, and CHD biomarkers is very scarce.

We used data from a population-based study to assess the association of the main drinking patterns and beverage preference with markers of lipid metabolism, hemostasis, inflammation, adipocyte function, and glucose metabolism.

Methods

Study participants

The main methods of the ENRICA study have been reported elsewhere [10]. In brief, this is a cross-sectional study conducted from 2008 to 2010 among 12,948 individuals representative of the non-institutionalized Spanish population aged ≥18 years. The sample was first stratified by province and size of municipality. Second, clusters were selected randomly in 2 stages: municipalities and census sections. Finally, the households within each section were selected by random telephone dialing using the directory of telephone land-lines. Information was collected in three stages. First, a phone interview on socio-demographic variables, lifestyle and diagnosed morbidity; second, a home visit to obtain blood and urine samples; and third, another home visit to obtain a diet history and to measure blood pressure and anthropometric variables.

The ENRICA protocol was approved by the clinical research ethics committees of the University Hospital *La Paz* in Madrid and Hospital *Clinic* in Barcelona.

Study variables

Drinking patterns

The average intake of alcohol was estimated using a diet history, developed from that used in the EPIC-cohort study in Spain, which assesses the regular consumption of alcoholic beverages in the preceding year[11]. Regular heavy alcohol intake was defined as ≥40 g/day in men and ≥24 g/day in women. Lower intakes were deemed to be regular moderate

intake[12]. Binge drinking was defined as the intake of ≥80 g of alcohol in men and ≥60 g in women in women at any given drinking session (the entire evening or night) during the preceding 30 days[13]. Non-drinkers included lifetime abstainers and sporadic drinkers.

Because the average alcohol ingested by a binge drinker can be either moderate or heavy, depending upon the alcohol intake on the rest of the drinking occasions, we classified individuals into six drinking patterns: 1) non-drinkers; 2) ex-drinkers; 3) moderate drinkers with no binge drinking (MNB); 4) moderate drinkers with binge drinking (MB); 5) heavy drinkers with no binge drinking (HNB); and, 6) heavy drinkers with binge drinking (HB).

Among drinkers, a preference for a specific type of alcoholic beverage (wine, beer or spirits) was deemed to exist when such drink accounted for over 80% of alcohol intake in the study participant.

Biomarkers of coronary heart disease

Biomarkers of coronary risk were measured in 12-hour fasting blood samples. Laboratory determinations were performed in the Center of Biological Diagnostics of the *Clínic* Hospital in Barcelona, using standardized procedures and appropriate quality controls. Biomarkers included total cholesterol, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), and triglycerides. We also assessed fibrinogen, which is a marker of hemostatic function, high-sensitivity C-reactive protein (hs-CRP), which is an indicator of chronic inflammation, and leptin, an adipocyte hormone.

As regards markers of glucose metabolism, we determined serum glucose, glycated hemoglobin (HbA1c), and insulin. The Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) index was calculated by multiplying glucose in mg/dl by insulin in mU/l and dividing by 405.

Potential confounders

We also assessed variables that are associated with drinking patterns and CHD biomarkers, including demographic variables, tobacco, physical activity and diet, which was assessed with a diet history[11]. Adherence to the Mediterranean diet was summarized with the index of Trichopoulou.

Weight and height were measured with standardized procedures, and body mass index (BMI) was calculated by dividing weight in kg by height in m squared.

Individuals reported physician-diagnosed morbidity and whether they were receiving lipid-lowering treatment. Finally, physical quality of life was summarized by the physical composite score on the SF-12 questionnaire.

Statistical analysis

Of the initial sample of 12,948 individuals, 11,380 provided information on alcohol drinking patterns and CHD biomarkers. Of these, we excluded 237 participants with cardiovascular disease, 777 without data on the study variables, and 10 with hs-CRP >10 mg/l because this level may result from an acute clinical episode. Thus, the main analyses were conducted with 10,356 individuals. In analyses with markers of glucose metabolism we additionally excluded 823 persons with diabetes mellitus, thus these analyses were based on 9,533 persons. The individuals excluded because of missing values were similar to those in the analytical sample except for age, which was five years higher in the excluded individuals.

To assess the study associations we used generalized linear regression models, where biomarkers of coronary risk were the dependent variable and the drinking patterns were the main independent variables. We used log-transformed serum concentrations of biomarkers to achieve normal distributions. The main results were expressed as the adjusted percentage

change, and 95% confidence interval (CI), in the geometric mean of each CHD biomarker, using non-drinkers as the reference group. The analyses were adjusted for the main confounders (please, see left column in table 1).

Similar analyses were conducted using beverage preference as the main independent variable, though in this case the regression models were additionally adjusted for binge drinking and the amount of alcohol intake with meals and without (continuous variable). These analyses were restricted to alcohol drinkers.

Analyses were performed using the survey procedures in Stata v.11.

Results

Among the study participants, 36.2% were non-drinkers, 5.0% ex drinkers, 47.8% MNB, 5.0% MB, 4.9% HNB, and 1.0% HB. Compared to non-drinkers, heavy and binge drinkers were more frequently men, with higher education and non-manual occupation. Also, they showed a higher fat and energy intake and a lower score on the Mediterranean diet index, did more physical activity at leisure time but less at home, and were more likely to smoke. Lastly, they showed a higher BMI, reported less morbidity, were less likely to have received lipid lowering treatment, and had a higher (better) score on the SF-12 (table 1).

Table 2 shows that, in comparison to non-drinkers, moderate and heavy drinkers had progressively higher levels of HDL-cholesterol, with an adjusted percentage change in geometric means ranging from 4.8% (95% CI 3.7 to 6.0%) in MNB to 9.6% (95% CI 5.1 to 14.2%) in HB. Because no substantial differences in total cholesterol or LDL-cholesterol were observed across drinking patterns, the LDL/HDL cholesterol ratio decreased from the MNB to the HB. Of note, this ratio tended to show relatively lower values in binge drinkers. No clear association was observed between drinking patterns and triglycerides, although the level

of triglycerides seemed to be somewhat higher in heavy drinkers. The results were similar when the analyses were repeated excluding individuals with lipid-lowering treatment.

Fibrinogen decreased progressively from the non-drinkers to the moderate and heavy drinkers: the adjusted change in geometric mean went from -2.2% (95% CI -3.1 to -1.3%) in MNB to -5.8% (95% CI -9.4 to -2.0%) in HB. hs-CRP was higher in HB than in non-drinkers, and leptin tended to decrease across most categories of drinkers, though the reduction achieved statistical significance only in HB. Ex-drinkers showed a higher level of fibrinogen and some suggestion of higher hs-CRP (table 2).

Both HbA1c and HOMA-IR showed lower values in most types of drinkers compared with non-drinkers. For HbA1c, the lowest values were observed in heavy drinkers regardless of binge drinking; for HOMA-IR, the lowest values were registered in binge drinkers and HNB (table 2).

Among the study drinkers (n=5,590), 33.9% did not show beverage preference, 36.3% preferred wine, 22.1% beer, and 7.6% spirits. The characteristics of study drinkers according to beverage preference are presented in table 3.

Table 4 shows that compared with drinkers with no beverage preference, those who preferred wine had a better lipid profile (lower total cholesterol, LDL-cholesterol and LDL/HDL-cholesterol ratio). Also, those with a preference for spirits showed lower total cholesterol and its fractions, with no difference in the LDL/HDL-cholesterol ratio; however they had higher levels of fibrinogen, HOMA-IR and hs-CRP, though statistical significance was not achieved in the latter case. No association was observed between beer preference and CHD biomarkers.

Discussion

Our study shows that regular moderate alcohol intake is associated with improved levels of several CHD biomarkers, specifically, higher HDL-cholesterol and lower fibrinogen, leptin, HbA1c and HOMA-IR. A similar or even more favorable impact on CHD biomarkers was observed for regular heavy drinking and binge drinking, with the exception of an increased hs-CRP in heavy-binge drinkers.

Our results on the elevation of HDL-cholesterol associated with moderate alcohol intake concur with those of a recent meta-analysis of short-term clinical trials[3]. A 4.3% (about 2.3 mg/dl) higher HDL-cholesterol in our study is close to the 3.7 mg/dl higher HDL-cholesterol found in clinical trials[3]. As regards heavy drinking, it has increased HDL-cholesterol in a few short-term clinical trials[5-7]. Our results extend the knowledge in this field by showing that in regular heavy and binge drinkers the elevation of HDL-cholesterol is even higher than in moderate drinkers, reaching an 8.5% increase with respect to non-drinkers. A cross-sectional analysis of data from adults in Belfast and in three cities in France also found a positive dose-response between HDL-cholesterol and alcohol up to an intake of >75 g/day[14]; moreover, in a population-based study in three Eastern European countries, heavy drinkers with at least one episode of binge drinking per month showed higher HDL-cholesterol than non-drinkers[15]. Although a meta-analysis of clinical trials provided some evidence of a dose-response elevation of HDL-cholesterol with alcohol intake[3], each alcohol dose corresponded to a different trial, so potential confounders such as smoking, physical inactivity, body weight, or diet could partly explain the dose-response. One advantage of our study and of the few other population-based investigations[14,15] is that information on the various drinking patterns is available from the same population.

As in clinical trials[3], we found no clear association between drinking patterns and LDL-cholesterol, but there was some tendency to lower levels in binge drinkers. Triglycerides also failed to show an association with moderate alcohol intake in clinical trials[3], in a

population-based study in Eastern Europe[15], and in our own study. Heavy drinking (>60 g/day) has been linked to higher triglycerides in some clinical trials[5,6] and in one population-based study[14], while in our study we found a non-statistically significant elevation in heavy and binge drinkers.

We found reduced levels of fibrinogen among drinkers, particularly heavy and binge drinkers. Compared to no alcohol use, moderate alcohol intake has been consistently associated with lower fibrinogen (-0.2 g/l) in clinical trials[3]. Results in the same direction have been observed in a cross-sectional analysis of the Framingham cohort[16]. As regards heavy drinking, in one randomized study consumers of 4 glasses of beer per day registered a 12% reduction of fibrinogen compared with non drinkers[17]. In the MONICA-Augsburg survey, alcohol intake up to 60 g/day was associated with reduced fibrinogen, but it increased at higher intake[18]. Also, in a cross-sectional study of older men, an increase in alcohol consumption from less than 1 drink/day to more than 5 drinks/day led to a significant decrease in fibrinogen[19]. While in most previous research results were similar for beer, wine and spirit drinkers[3,16], in our study individuals who preferred spirits showed higher fibrinogen levels.

As in clinical trials[3], we did not find an association between alcohol intake and hs-CRP, with the exception of heavy-binge drinkers and those who preferred spirits, where higher hs-CRP was observed. In cross-sectional studies, moderate drinkers usually have lower hs-CRP than non drinkers[20,21]. However, there is some observational evidence of a U-shaped relation between alcohol intake and CRP, whereby heavy drinkers show higher CRP than moderate drinkers and nondrinkers[22], a finding that is consistent with ours. In observational studies, differences in CRP level between drinkers of different types of beverages were small, although some tendency was observed to higher CRP among liquor drinkers[23], as in our study.

We observed that leptin tended to be lower in drinkers than in non-drinkers. The two clinical trials that have assessed the effect of alcohol on leptin have obtain conflicting results[3]. As regards cross-sectional studies, one has found a direct association between alcohol and leptin[24], while other study has found an inverse relation[25].

In experimental [26] and observational studies[27] alcohol consumption have shown a beneficial glycemic effect, partly mediated by increased insulin sensitivity. Moreover, moderate alcohol intake (<50 g/day) may reduce the risk of type 2 diabetes[28]. Therefore, our results concur with the existing literature. However, we are not aware of studies on binge drinking and glycemic control that can be compared with our results.

In analyses adjusted for binge drinking and volume of alcohol, wine preference was associated with better lipid profile while spirits preference was linked to worse levels of fibrinogen and HOMA-IR. Our results on wine preference and lipid biomarkers concur with those from clinical trials, because most of them used wine as the alcohol intervention[3]. Also, a recent observational study has found that heavy drinking, particularly among heavy liquor drinkers, increases plasma glucose[29].

This study has several strengths and limitations. Among its strengths are the large size and the representativeness of the adult population of a whole country. Also, the study included complete characterization of alcohol consumption, differentiating between never and former drinkers, and including a comprehensive classification of consumption patterns. Among the limitations, the most important are the cross-sectional design and the fact that alcohol consumption was self-reported. Thus, the study design precludes causal attribution for the observed associations. Furthermore, although we have adjusted the models for many potential confounders, we cannot rule out that some of the observed associations could be driven by residual confounding. Lastly, as observed in other studies, it is possible than the better lipid

profile of wine drinkers could be partly due to healthier lifestyles not considered in the analyses.

We conclude that, in a free-living population, moderate alcohol intake is associated with improved levels of HDL-cholesterol, fibrinogen and markers of glucose metabolism. Therefore, it is consistent with the reduced coronary risk associated with moderate consumption of alcoholic beverages in many longitudinal studies. However, heavy and binge drinking were associated with similar or even more favorable levels of CHD biomarkers. This suggests that the excess CHD risk observed among irregular heavy drinkers in some studies may be due to mechanisms other than those studied in this work. Finally, since heavy and binge drinking produce substantial health harms, our results should not be used to promote alcohol consumption[30].

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