Relation Between Alcohol Consumption and C-Reactive Protein Levels in the Adult US Population

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Background: **Moderate alcohol consumption has been linked to a decreased risk of cardiovascular death. Systemic inflammation as indicated by elevated levels of C-reactive protein might play a role in this relation.**

Methods: **To evaluate the association of alcohol consumption with C-reactive protein, we analyzed the findings of the Third National Health and Nutrition Examination, a population-based survey representing the noninstitutionalized US population. Participants were aged 17 and older (n = 11,572). The main outcome measures studied were probability of C-reactive protein measurements being greater than 0.30 mg/dL (corresponding to the 75th percentile for the population) stratified by categories of alcohol consumption. Multivariate logistic regression was used to adjust for potential confounders.**

Results: **Among nondrinkers 31% had elevated C-reactive protein levels, compared with 21% of low-to-moderate–frequency drinkers and 18% of high-frequency drinkers. In a model adjusted for confounding variables, those who drank 1 to 10 times per month (OR 0.83, 95% CI 0.72–0.95), 11 to 30 times (OR 0.74, 95% CI 0.62–0.88), and more than 60 times per month (OR 0.67, 95% CI 0.48–0.93) were less likely than nondrinkers to have elevated C-reactive protein levels.**

Conclusions: **Alcohol consumption is associated with a decreased probability of elevated C-reactive protein levels. This association supports an anti-inflammatory mechanism by which moderate alcohol use might protect against cardiovascular death. (J Am Board Fam Pract 2002;15:437–42.)**

Light to moderate consumption of ethanol has consistently been linked to a decrease in cardiovascular disease mortality, as reviewed elsewhere.[1] A protective effect of alcohol use on cardiovascular disease is suggested by the consistency of the epidemiologic evidence, as well as findings that show metabolizers of alcohol are more likely to experience a decrease in the incidence of myocardial infarction.[2] Additional evidence indicates that current drinkers who have a myocardial infarction have a better prognosis than alcohol abstainers.[3]

Clinicians are now faced with the increasingly challenging dilemma of deciding whether light to moderate alcohol use might be beneficial for patients at higher risk of coronary artery disease. Although most experts would not currently support recommending alcohol use to abstainers,[4] improved knowledge of the mechanisms by which alcohol protects against ischemic heart disease death is needed to aid in determining who is most and least likely to benefit from light drinking. Earlier studies suggest that increases in high-density lipoprotein (HDL)-cholesterol could account for approximately 50% of the protective effect of alcohol,[5,6] but it is clear that other factors are involved. If the beneficial effects of alcohol are mediated through established risk factors, epidemiologic studies should discern an association between alcohol use and the risk factors.

C-reactive protein is an acute phase reactant and marker of underlying systemic inflammation.[7] Circulating at low concentrations in healthy individuals, it rises dramatically in response to infection, inflammation, and injury. During the last decade, evidence has accumulated that an elevated level of C-reactive protein is an independent risk factor for myocardial infarction and peripheral vascular disease.[8,9] This understanding has paralleled the recognition of atherosclerosis as a systemic inflam-

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matory disease.[10] Some epidemiologic evidence suggests that the protective effect of alcohol on ischemic heart disease death might be partially mediated through an anti-inflammatory action of alcohol.[11] We undertook this cross-sectional study to determine the association of alcohol use with C-reactive protein levels in a sample representative of the US population. Positive findings from this study would provide additional support for an anti-inflammatory effect of alcohol. Negative findings would suggest the need for reconsideration of the anti-inflammatory hypothesis and indicate that other potential mechanisms for the beneficial effects of light to moderate alcohol consumption need to be explored.

Methods

This study is an analysis of data from the Third National Health and Nutrition Examination Survey (NHANES III). This survey collected multistage, stratified, clustered samples from a civilian, noninstitutionalized population from 1988 to 1994.

The household adult data file contains the results of the questionnaire administered to all adults in the survey population. All surveyed residents were invited to participate in additional data collection, including physical examination and laboratory measures. The examination and laboratory data files contain the results of the examinations and laboratory tests performed on survey participants who followed up their household interview as requested. More detailed information on the plan and operation of the NHANES III has been previously published.[12,13]

After merging the three data files containing the variables needed for the study, complete data were available from 11,572 adults (≥17 years of age). Using the NHANES III and the appropriate weights allowed us to make estimates for the entire noninstitutionalized adult US population.

Dependent Variable

C-reactive protein was measured as part of the NHANES III physical and laboratory examination. Standard phlebotomy techniques were used to obtain specimens. Serum specimens were frozen to −20°C until used for laboratory analysis. C-reactive protein was analyzed using a fully automated Behring Nephelometer Analyzer System (Behring Diagnostics, Inc, Somerville, NJ). Further details about the specific methods used in the laboratory procedures of the NHANES III are available elsewhere.[13]

In the current study, the population distribution indicated that a C-reactive protein of 0.30 mg/dL corresponded to the 75th percentile. We considered any value above 0.30 mg/dL as elevated C-reactive protein.

Independent Variable

Alcohol use was assessed in terms of patient self-report of drinking frequency in the last month. This frequency was measured as the sum of three questions focusing on consumption of (1) beer and light beer; (2) wine, wine coolers, sangria, and champagne; and (3) hard liquor, such as tequila, gin, vodka, scotch, rum, whiskey, and liqueurs. The frequency of alcohol consumption was not normally distributed. Consequently, we collapsed alcohol use into categories of drinking episodes in the last month: 0, 1 to 10, 11 to 30, 31 to 60, and more than 60 drinking episodes.

Control Variables

Standard demographic indicators (age, sex, race-ethnicity) were included as control variables. We also controlled for factors that might confound investigations of systemic inflammation. Body mass index (BMI) and current smoking status have been associated with C-reactive protein levels.[14,15] BMI was measured as part of the clinical examination phase of the NHANES III. Current smoking status was assessed through a patient self-report. Additional control variables were self-reports of whether a physician had ever told the respondent that he or she had an autoimmune disorder, such as lupus or rheumatoid arthritis. Additionally, use of either prescribed anti-inflammatory medications (eg, corticosteroids, nonsteroidal anti-inflammatory medications) or other over-the-counter medicines with anti-inflammatory properties (eg, aspirin, ibuprofen) taken within the past month were assessed.

Analysis Plan

Variables were weighted to account for the complex sampling design of the NHANES III. As a result, the computed analyses are population estimates for the noninstitutionalized adult population.

We initially performed descriptive statistics. Diagnostic statistics indicated that both alcohol use

Table 1. Population Characteristics of Adults 17 and Older from the NHANES III.

Characteristic	Value
Sex (% male)	48.0
Race-ethnicity (%)	
Non-Hispanic white	76.3
Non-Hispanic black	10.6
Mexican American	5.2
Other	7.8
Alcohol use drinking frequency per month (%)	
0	45.4
1 to 10	31.0
11 to 30	16.6
31 to 60	5.0
More than 60	2.0
Drinking frequency per month (mean ± SE)	8.4 ± 0.3
BMI greater than or equal to 25 (%)	53.9
C-reactive protein, 75th percentile (mg/dL)	0.3
Smoking status	
Current smoker (%)	28.1
Number of cigarettes per day (mean ± SE)	19.0 ± 0.4
Age, years (mean ± SE)	43.3 ± 0.4
Autoimmune disease (%)	3.6
Using anti-inflammatory medicine in past month (%)	57.5

NHANES III—Third National Health and Nutrition Examination Survey.

and C-reactive protein had nonnormal distributions, so both were used as categorical variables. Chi-square analyses were computed for the relation between alcohol use and C-reactive protein levels. A logistic regression with alcohol use and C-reactive protein was used to compute the unadjusted relation between alcohol use and elevated C-reactive protein levels and the corresponding odds ratios. A second forced-inclusion logistic regression model was computed to determine the independent association between alcohol use and likelihood of having elevated C-reactive protein levels while controlling for age, sex, BMI, race-ethnicity, presence of autoimmune disease (lupus or rheumatoid arthritis), being a current smoker, and current use of prescribed or over-the-counter anti-inflammatory medicine in the past month.

Results

The characteristics of the population are displayed in Table 1. The data indicate that abstainers from alcohol comprise the largest category of alcohol use and account for almost one half of the population. Furthermore, more than one half of the population currently uses some type of anti-inflammatory medication, either over-the-counter or prescribed.

Abstainers from alcohol are more likely to have elevated C-reactive protein levels than those who consume alcohol. Table 2 explores this relation and indicates that C-reactive protein levels drop significantly with the use of alcohol, and minor differences occur within alcohol consumption categories. For women and Mexican Americans, the association between alcohol consumption categories and the proportion of individuals with elevated C-reactive protein levels resulted in U-shaped curves, with the probability of elevated levels increasing in the most frequent drinkers compared with moderate- and low-frequency drinkers.

Table 3 displays both unadjusted and adjusted odds ratios for the likelihood of having elevated C-reactive protein levels by different amounts of alcohol consumption. In the adjusted model controlling for relevant confounding variables, individuals in all categories of alcohol use, except for 31 to 60 drinks per month category, are significantly less

Table 2. Relation of Monthly Alcohol Intake to Population Percentage with Elevated C-Reactive Protein.

	Drinking Frequency per Month					
Characteristic	0	1–10	11–30	31–60	61+	*P**
All	30.7	22.4	18.1	19.5	17.5	<.01
Sex						
Male	23.6	19.0	14.2	19.1	15.6	<.01
Female	35.0	25.7	25.0	20.4	29.1	<.01
Race-ethnicity						
Non-Hispanic white	30.6	21.2	17.0	18.5	14.0	<.01
Non-Hispanic black	37.2	32.5	27.3	28.9	25.1	<.01
Mexican American	33.9	21.1	20.0	21.5	25.5	<.01
Other	22.0	23.3	17.1	16.2	43.2	.79

**P* value for Wald chi-square test.

Table 3. Unadjusted and Adjusted Relations Between Alcohol Intake on C-Reactive Protein.

Model	Monthly Drinking	Odds Ratio†	95% Confidence Interval		*P**
			Lower Limit	Upper Limit	
Unadjusted	1–10	0.65	0.57	0.74	<.01
	11–30	0.50	0.42	0.59	
	31–60	0.55	0.41	0.73	
	61+	0.48	0.33	0.69	
Adjusted‡	1–10	0.83	0.72	0.95	<.01
	11–30	0.74	0.62	0.88	
	31–60	0.80	0.59	1.10	
	61+	0.67	0.48	0.93	

**P* value of Wald F main effects test.
†Reference groups: Nondrinkers.
‡Adjusted for sex, race-ethnicity, age, body mass index, autoimmune disease status, anti-inflammatory medications, and current smoking status.

likely to have elevated C-reactive protein levels when compared with those who abstain from alcohol. The 95% confidence intervals for the drinking categories incorporate a similar range of values.

Discussion

This cross-sectional analysis shows that low-, moderate-, and high-frequency alcohol consumption is associated with a significantly decreased probability of having an elevated level of C-reactive protein in the adult US population. An inverse association between alcohol use and likelihood of having elevated C-reactive protein levels remained even after adjusting for potential confounding caused by age, body mass index, sex, race, current smoking status, self-report of autoimmune disease, and use of anti-inflammatory medications.

In addition to evaluating the population-wide association of C-reactive protein level and alcohol consumption, we also performed stratified analyses to assess the association of C-reactive protein level with alcohol use by sex and race. The increased tendency of abstainers to have elevated C-reactive protein levels held for all groups analyzed, including men, women, non-Hispanic blacks, Mexican Americans, and non-Hispanic whites. The association of C-reactive protein and alcohol use for Mexican Americans and women was weakly U-shaped, with the highest frequency drinkers being more likely than moderate drinkers to have elevated C-reactive protein levels. Even in these groups however, the most frequent drinkers remained less likely than abstainers to have elevated C-reactive protein levels.

Our definition of elevated C-reactive protein at 0.30 mg/dL is conservative for the purpose of suggesting elevated levels and strengthens the conclusions of a relation between alcohol and C-reactive protein levels. In a recent study of risk factors for systemic atherosclerosis, individuals with peripheral arterial disease had median C-reactive protein levels of 0.14 mg/dL, whereas individuals without peripheral arterial disease had significantly lower median levels of 0.10 mg/dL.[9]

Findings in this study are generally similar to those in a recently published cross-sectional analysis of a cohort of individuals in western Germany.[11] These investigators found an overall inverse association of C-reactive protein and alcohol use, with abstainers tending to have higher C-reactive protein levels when compared with light and moderate drinkers. In men, a weak U-shaped association was found, with C-reactive protein levels increasing in the heaviest drinkers. While this U-shaped curve fits well with the epidemiologic association of alcohol and coronary mortality, it was not statistically significant.

Our study supports the finding that light and moderate drinkers are more likely than nondrinkers to have lower C-reactive protein levels, but we did not find a U-shaped relation for the overall population or in men. This difference might be due to different measures of alcohol use, which in our study is frequency related rather than quantity. In addition, we were unable to analyze the entire range of C-reactive protein. Because of issues in the precision of measures used to assess C-reactive protein, the NHANES III used a lower cutoff of 0.21 mg/dL and reported that value for anyone at or

below 0.21 mg/dL. If we had information for the full range of C-reactive protein, we might have found that levels in high-frequency drinkers were on average higher than in drinkers of low to moderate frequency, but still within the 75th percentile.

Strengths of this analysis include the use of a large, nationally representative sample, allowing for overall population estimates as well as populations of special interest. We also designed this study to adjust specifically for potential confounders of the C-reactive protein and alcohol association based on a review of the epidemiologic literature on C-reactive protein.

There are several limitations of this study that should be noted. First, although this study suggests that an anti-inflammatory effect of alcohol might exist, we cannot draw any conclusions regarding the contribution of this effect to the prevention of ischemic heart disease. In addition, because of the cross-sectional study design, we are unable to conclude firmly that alcohol drinking is the cause of the decreased prevalence of highest quartile C-reactive protein levels. Confounding from unknown factors could explain the association, and there might be no independent relation between alcohol use and C-reactive protein levels. Despite these limitations, the wealth of evidence pointing toward a protective effect of alcohol on ischemic heart disease death makes this association with C-reactive protein of particular interest.

An additional limitation is the reliance on self-report to determine alcohol use, use of anti-inflammatory medications, tobacco use, and the presence of systemic autoimmune disease. If underreporting of alcohol consumption were common, the inverse association of alcohol use and C-reactive protein levels would still hold true in this study population, because compared with abstainers, all categories of alcohol consumers had a decreased probability of high C-reactive protein levels. It also should be clearly recognized that the alcohol consumption categorization is a frequency measure rather than a quantity measure. Although frequency and quantity are almost certainly correlated, a similar analysis using valid quantity estimates and controlling for pattern of use might yield different results.

Although we are unable to comment firmly on the mechanism by which alcohol protects against ischemic heart disease death and myocardial infarction, these and other findings suggest that a systemic anti-inflammatory effect might exist. The strength of the evidence, however, does not justify recommending moderate alcohol use to patients with elevated C-reactive protein levels, and more specific, prospective studies are needed. To date one small crossover trial has evaluated the effect of moderate alcohol use on C-reactive protein levels and found that moderate drinking did result in a decrease in C-reactive protein levels among healthy volunteers.[16] A direction for future research might include additional experimental studies designed specifically to test the effect of alcohol on levels of inflammatory markers. Although such studies would not conclusively show that a reduction in ischemic heart disease incidence and death would occur as a result of an anti-inflammatory effect of alcohol, they might provide stronger evidence that this mechanism is one (in addition to increases in HDL-cholesterol) by which alcohol use might be protective.

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