Impact of Inflammation on the Relationship Among Alcohol Consumption, Mortality, and Cardiac Events

The Health, Aging, and Body Composition Study

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Background: Uncertainty remains about the overall survival benefit of alcohol consumption and the mechanisms underlying the cardioprotective effect of light to moderate alcohol intake. Recent evidence suggests an anti-inflammatory effect of light to moderate alcohol consumption. We investigated the relationship of alcohol intake with all-cause mortality and cardiac events and evaluated whether this relationship is mediated or modified by inflammatory markers.

Methods: The analysis included 2487 subjects, aged 70 to 79 years, without baseline coronary heart disease (CHD) or heart failure (HF), participating in the Health, Aging, and Body Composition study. All-cause mortality and incident cardiac events (CHD and HF) were detected during a mean follow-up of 5.6 years. Alcohol consumption and serum levels of interleukin-6 (IL-6) and C-reactive protein (CRP) were assessed at baseline.

Results: A total of 397 participants died, and 383 experienced an incident cardiac event. Compared with never or occasional drinkers, subjects drinking 1 to 7 drinks per week had lower age-, sex-, and race-adjusted incidences of death (27.4 vs 20.1 per 1000 person-years, respectively) and cardiac events (28.9 vs 20.8 per 1000 person-years). After adjustment for confounders, compared with never or occasional drinkers, light to moderate drinkers (1-7 drinks per week) showed a decreased risk of death (hazard ratio [HR], 0.75; 95% confidence interval [CI], 0.56-1.00) and cardiac events (HR, 0.72; CI, 0.54-0.97). Adjustment for potential mediators, and particularly inflammatory marker levels, did not affect the strength of this association.

Conclusion: Light to moderate alcohol consumption was associated with significantly lower rates of cardiac events and longer survival, independent of its anti-inflammatory effect.

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Several studies suggest that light to moderate alcohol consumption is associated with a reduced mortality rate.1,2 This survival benefit has been attributed to the reduced risk of cardiovascular disease (CVD), primarily owing to the protective effect of moderate alcohol consumption on coronary heart disease (CHD).3,4 Moreover, recent studies suggest that moderate alcohol intake is also associated with a decreased risk of heart failure (HF).5 On the other hand, alcohol can substantially increase the incidence of severe chronic diseases,6,7 and uncertainty remains about the overall survival benefit of alcohol consumption.8 In addition, the net balance between risk and benefit is likely to vary as a function of age, sex, and background cardiovascular risk, with greater benefit seen among subjects at increased CVD risk.9,10

The protective effect of light to moderate alcohol consumption on CVD has been related to changes in serum lipid levels, hemostatic factors, and insulin resistance; nevertheless, the underlying mechanisms remain unclear. There is strong evidence that increased levels of inflammatory markers, including C-reactive protein (CRP) and interleukin-6 (IL-6), predict the onset of cardiovascular events and mortality, identifying subjects at increased CVD risk.11,12 Recent studies have shown that light to moderate alcohol intake is associated with lower levels of acute-phase markers, including IL-6 and CRP,13,14 and it has been suggested that ethanol might modulate IL-6 production and/or action at several sites.15 These findings suggest that the protective effect of moderate alcohol consumption on health-related outcomes may be mediated through an anti-inflammatory effect. Moreover, it may also be hypothesized that the effect of moderate alcohol consumption may be modified by the level of inflammatory markers, which is expression of a different background CVD risk.

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In the present study, we investigated the relationship between alcohol consumption, all-cause mortality, and cardiac events (CHD and HF) in a sample of well-functioning, CVD-free older persons, and we evaluated whether this relationship is mediated or modified by serum inflammatory marker (IL-6 and CRP) levels.

**METHODS**

**SAMPLE**

Data are from 3075 well-functioning subjects participating in the Health, Aging, and Body Composition study. Participants aged 70 to 79 years were recruited between April 1997 and June 1998 from a random sample of white and black Medicare-eligible adults living in designated ZIP codes from the metropolitan areas surrounding the 2 field centers (Pittsburgh, Pa, and Memphis, Tenn). Eligibility criteria included (1) no difficulty walking 1/4 of a mile, climbing 10 steps, or performing basic activities of daily living; (2) no life-threatening illness; and (3) no plans to leave the area for 3 years. The presence of clinical disease at baseline was ascertained by use of an algorithm based on self-reported physician-diagnosed disease information and medication use, mirroring adjudicated diagnoses in the Cardiovascular Health Study. The present analyses are based on 2487 participants; 576 subjects were excluded due to prevalent CHD or HF at baseline, and 12 for missing data on alcohol consumption. Each participant provided written informed consent. The study protocol was approved by the institutional review boards of the University of Pittsburgh and the University of Tennessee.

**ALCOHOL INTAKE**

Information on alcohol consumption was assessed by means of a questionnaire administered at the baseline interview, as previously described. The interviewer explained to the participant that alcoholic beverages should include any kind of drink containing alcohol, including beer, wine, liquors, and cocktails or other mixed drinks. The interviewer also explained that 1 drink was considered to be equal to 12 ounces of beer (1 can), 5 ounces of wine (1 full glass), or a drink containing a “shot,” a “jigger,” or a “finger” of liquor. After that, the participant was asked to report how many drinks he/she had in a typical week over the past 12 months. Using this information, weekly alcohol intake was categorized as follows: former, never or occasional (<1 drink per week), light to moderate (1-7 drinks per week), and heavier (more than 7 drinks per week). For non-drinkers (former and never drinkers), the reason for not drinking was also collected, and the following primary reasons were considered: no need, dislike, medical reasons/health status, religiosity/moral, recovering alcoholic, family member alcoholic, cost, or other.

**OUTCOMES**

During the study follow-up, participants were contacted by telephone every 6 months and had a clinical visit every year, during which health status was assessed and data about interim hospitalizations or major outpatient procedures were collected. When an event was reported, hospital records were collected and verified by a disease adjudicator at each site. The study outcome measures were all-cause mortality and a composite outcome of cardiac events. Date and immediate and underlying causes of death were verified and ascertained from the death certificate, hospital records, and proxy interviews. The cardiac event outcome was defined as any incident fatal event or overnight hospitalization in an acute-care hospital for myocardial infarction, angina, or HF. Coronary heart disease and HF incident events were also considered as separate outcomes in secondary analyses. If a participant had a CHD and an HF event concurrently, both events were coded.

Follow-up time was defined as the time from the baseline visit until the first event date (death or cardiac event). For those who did not have any event or were lost to follow-up, the follow-up time was censored at the last contact date.

**INFLAMMATORY MARKERS**

Interleukin 6 and CRP levels were obtained from frozen stored serum collected after an overnight fast at baseline. Interleukin 6 and CRP levels were measured in duplicate by an HS600 Quantikine enzyme-linked immunosorbent assay (ELISA) kit from R&D Systems (Minneapolis, Minn). The detectable limit for IL-6 (by ELISA) was 0.10 pg/mL. Serum levels of CRP were also measured in duplicate by ELISA based on purified protein and polyclonal anti-CRP antibodies (Calbiochem, San Diego, Calif). The CRP assay was standardized according to the World Health Organization First International Reference Standard, with a sensitivity of 0.08 mg/L. The lower detection limit for CRP was 0.007 mg/L. Assays of blind duplicates collected for 150 participants yielded an average interassay coefficient of variation of 10.3% for IL-6 and 8.0% for CRP.

**OTHER COVARIATES**

The following variables were considered as covariates: age, sex, race, study site, level of education, smoking history (never, former, or current smoker), physical activity, body mass index (calculated as weight in kilograms divided by the square of height in meters), visceral fat area (measured in square centimeters from a computed tomography image obtained at L4-L5), ankle brachial index, biological markers, comorbidity (adjudicated presence of diabetes, hypertension, cerebrovascular disease, and cancer), and medication use.

Physical activity performed during the last 7 days was assessed. Time spent on high-intensity and moderate-intensity exercise activities was determined as well as information on the intensity level. A metabolic equivalent value was assigned to each activity/intensity combination. Participants were categorized as physically inactive if they expended less than 336.8 /wk. The ankle brachial index was calculated by the systolic blood pressure of the ankle divided by the systolic blood pressure of the arm and was used as an indicator of atherosclerosis severity. Levels of total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides, serum albumin, and creatinine were measured on a Vitros 950 analyzer (Johnson & Johnson, Piscataway, NJ). Low-density lipoprotein cholesterol level was calculated using the Friedwald equation. For hemoglobin A1c analysis, ion-exchange high-performance liquid chromatography was used (Biorad Variant analyzer; Hercules, Calif).

Current use of anti-inflammatory drugs (nonsteroidal, salicylates, and other anti-inflammatory drugs) as well as statins was determined from drug data coded using the Iowa Drug Information System ingredient codes.

**STATISTICAL ANALYSIS**

Main characteristics of the sample population were compared across alcohol consumption categories using the chi-square test for proportions and analysis of variance for continuous variables. Interleukin 6 and CRP values were log-transformed to achieve an approximately normal distribution. Direct standardization was used to obtain age-, sex-, and race-adjusted incidence rates per 1000
RESULTS

The mean age of the study sample was 73.5 years; 55% were women, and 41.8% were black. Almost 50% of the participants never drank alcohol or drank less than 1 drink per week during the last 12 months. About 22% of study participants reported the consumption of some amount of alcohol in the past but not current consumption. Only 7.7% of this cohort reported consuming more than 7 drinks per week. Women were more likely to be never or occasional drinkers (Table 1).

During a mean follow-up time of 5.6 years, a total of 397 participants died, and 383 experienced an incident event. The HR was calculated relative to never drinkers (1 drink per week), as preliminary data on inflammatory markers and cardiovascular risk factors as high level (above the median) and low level (below the median). The low number of events in women did not allow us to further stratify by the inflammatory markers level; thus, these analyses were performed only in men. The presence of a significant interaction between alcohol consumption and sex, race, and inflammatory marker level was tested by means of the likelihood ratio test.

Two different analytic models were created as follows: (1) adjusted for demographic variables (age, sex, race, and site); (2) additional adjustment for lifestyle variables (education, smoking status, and physical activity). To investigate the effects of cardiovascular risk factors and inflammatory markers on the studied relationship, the following variables were added successively, 1 at a time, to the second model: HDL-C, low-density lipoprotein-cholesterol, triglycerides, diabetes, hypertension, ankle brachial index, body mass index, visceral fat, IL-6, and CRP. Finally, the fully adjusted model was tested. Stratified analyses were conducted to determine whether the effect of alcohol consumption was modified by inflammatory marker levels. For this purpose, IL-6 and CRP levels were categorized as high level (above the median) and low level (below the median).

The associations of alcohol consumption with mortality and cardiac events, according to baseline alcohol consumption categories, were modeled by Cox proportional hazard regression analysis by using a multivariate regression model including alcohol consumption as linear and quadratic terms and tested using likelihood ratio test. The assumption of proportionality was assessed through the analysis of Schoenfeld residuals. Scattered analyses showed no risk difference between these 2 groups. The analyses were performed only in men. The presence of a significant interaction between alcohol consumption and sex, race, and inflammatory marker level was tested by means of the likelihood ratio test.

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cardiac event. Figure 1 shows the nonlinear relationship between alcohol consumption and the age-, sex-, and race-adjusted incidence of all-cause mortality (quadratic term, \( P = .008 \)) and cardiac events (quadratic term, \( P = .04 \)). The rates of death and cardiac events were lowest among subjects drinking 1 to 7 drinks per week. A similar nonlinear relationship was observed when CHD and HF incidences were analyzed separately.

Multivariate analyses confirmed the presence of a J-shaped relationship between alcohol consumption and all-cause mortality (Table 2). Compared with never and occasional drinkers, light to moderate drinkers (1-7 drinks per week) appeared to have a lower risk of all-cause mortality (model 1: HR, 0.82; 95% confidence interval [CI], 0.62-1.09), whereas heavier drinkers had an increased risk of death (HR, 1.56; 95% CI, 1.10-2.21). After accounting for lifestyle variables (model 2), light to moderate alcohol consumption was associated with a more pronounced death risk reduction (HR, 0.75; 95% CI, 0.56-1.00). Additional inclusion in this model of potential mediating factors such as HDL-C, diabetes, and hypertension did not substantially affect the strength of the relationship (Table 3). In particular, after inclusion of IL-6 (HR, 0.75; 95% CI, 0.56-1.00) and CRP (HR, 0.73; 95% CI, 0.55-0.98), light to moderate alcohol consumption remained associated with a substantial death risk reduction that persisted in the fully adjusted model (HR, 0.74; 95% CI, 0.55-0.99). Conversely, the increased risk of all-cause mortality in subjects drinking more than 7 drinks per week was attenuated after adjustment. Survival analysis was then conducted separately for cardiovascular and noncardiovascular mortality. We observed that light to moderate alcohol consumption was associated with a lower risk of both cardiovascular mortality (94 events; HR, 0.68; 95% CI, 0.37-1.27) and noncardiovascular mortality (303 events; HR, 0.75; 95% CI, 0.54-1.05), but the results were not statistically significant.

We found a U-shaped relationship between alcohol intake and cardiac events. Relative to never or occasional drinkers, light to moderate drinkers had an almost 30% risk reduction of cardiac events (Table 2) (model 2: HR, 0.72; 95% CI, 0.54-0.97), even after controlling for cardiovascular risk factors and inflammatory markers (Table 3). Consistent results were found after exclusion of 171 participants who were not drinking for health-related conditions.

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**Figure 1.** Age-, sex-, and race-adjusted incidence per 1000 person-years of coronary heart disease (CHD), heart failure (HF), all-cause deaths, and cardiac events (defined as fatal and nonfatal CHD and HF) according to alcohol consumption categories.

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Analyses stratified by sex showed that in men, light to moderate alcohol consumption appeared strongly associated with a decreased risk of both all-cause mortality (HR, 0.62; 95% CI, 0.43-0.90) and cardiac events (HR, 0.63; 95% CI, 0.43-0.92). Among women, light to moderate alcohol consumption was associated with a slightly nonsignificant cardiac event risk reduction (HR, 0.85; 95% CI, 0.52-1.36), and the risk of all-cause mortality was not affected.

### Table 2. Hazard Ratios (95% Confidence Intervals) of All-Cause Mortality and Cardiac Events by Alcohol Consumption in 2487 Subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Never/≤1 (n = 1221)</th>
<th>Former (n = 535)</th>
<th>1-7 (n = 539)</th>
<th>&gt;7 (n = 192)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events, No.</td>
<td>181</td>
<td>105</td>
<td>68</td>
<td>43</td>
</tr>
<tr>
<td>Model 1*</td>
<td>1</td>
<td>1.19 (0.93-1.52)</td>
<td>0.82 (0.62-1.09)</td>
<td>1.56 (1.10-2.21)</td>
</tr>
<tr>
<td>Model 2†</td>
<td>1</td>
<td>1.11 (0.87-1.43)</td>
<td>0.75 (0.56-1.00)</td>
<td>1.36 (0.95-1.95)</td>
</tr>
<tr>
<td>Cardiac events (CHD and HF incident events)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events, No.</td>
<td>180</td>
<td>95</td>
<td>68</td>
<td>40</td>
</tr>
<tr>
<td>Model 1*</td>
<td>1</td>
<td>1.11 (0.86-1.44)</td>
<td>0.74 (0.56-0.99)</td>
<td>1.23 (0.86-1.76)</td>
</tr>
<tr>
<td>Model 2†</td>
<td>1</td>
<td>1.05 (0.81-1.36)</td>
<td>0.72 (0.54-0.97)</td>
<td>1.14 (0.79-1.85)</td>
</tr>
</tbody>
</table>

Abbreviations: CHD, coronary heart disease; HF, heart failure.
*Adjusted for age, sex, race, and site.
†Adjusted for age, sex, race, site, education, smoking status, and physical activity.

### Table 3. Impact of Cardiovascular Risk Factors and Inflammatory Markers on the Association Between Alcohol Consumption, Mortality, and Cardiac Events*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Never/≤1 (n = 1221)</th>
<th>Former (n = 535)</th>
<th>1-7 (n = 539)</th>
<th>&gt;7 (n = 192)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-Cause Mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2 plus:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-C</td>
<td>1.00</td>
<td>1.11 (0.87-1.43)</td>
<td>0.75 (0.56-1.01)</td>
<td>1.40 (0.98-2.01)</td>
</tr>
<tr>
<td>LDL-C</td>
<td>1.00</td>
<td>1.11 (0.86-1.42)</td>
<td>0.75 (0.56-1.00)</td>
<td>1.35 (0.94-1.93)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.00</td>
<td>1.12 (0.87-1.43)</td>
<td>0.75 (0.56-1.01)</td>
<td>1.37 (0.96-1.96)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.00</td>
<td>1.08 (0.84-1.39)</td>
<td>0.76 (0.57-1.01)</td>
<td>1.40 (0.98-2.00)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.00</td>
<td>1.11 (0.86-1.42)</td>
<td>0.75 (0.56-1.00)</td>
<td>1.37 (0.96-1.95)</td>
</tr>
<tr>
<td>ABI</td>
<td>1.00</td>
<td>1.09 (0.85-1.40)</td>
<td>0.75 (0.56-1.01)</td>
<td>1.34 (0.94-1.92)</td>
</tr>
<tr>
<td>BMI</td>
<td>1.00</td>
<td>1.11 (0.86-1.42)</td>
<td>0.75 (0.56-1.00)</td>
<td>1.35 (0.95-1.94)</td>
</tr>
<tr>
<td>Visceral fat</td>
<td>1.00</td>
<td>1.11 (0.87-1.43)</td>
<td>0.75 (0.56-1.00)</td>
<td>1.35 (0.94-1.93)</td>
</tr>
<tr>
<td>IL-6</td>
<td>1.00</td>
<td>1.09 (0.85-1.40)</td>
<td>0.75 (0.56-1.00)</td>
<td>1.25 (0.87-1.79)</td>
</tr>
<tr>
<td>CRP</td>
<td>1.00</td>
<td>1.11 (0.86-1.42)</td>
<td>0.73 (0.55-0.98)</td>
<td>1.30 (0.91-1.87)</td>
</tr>
<tr>
<td>Model 2 plus potential confounders†</td>
<td>1.00</td>
<td>1.08 (0.84-1.39)</td>
<td>0.75 (0.56-1.00)</td>
<td>1.42 (0.99-2.03)</td>
</tr>
<tr>
<td>Fully adjusted model‡</td>
<td>1.00</td>
<td>1.03 (0.79-1.32)</td>
<td>0.74 (0.55-0.99)</td>
<td>1.22 (0.84-1.77)</td>
</tr>
</tbody>
</table>

| Cardiac Events (CHD and HF incident Events) |                     |                  |               |              |
| Model 2 plus:                           |                     |                  |               |              |
| HDL-C                                   | 1.00                | 1.04 (0.80-1.35) | 0.73 (0.55-0.98) | 1.19 (0.82-1.73) |
| LDL-C                                   | 1.00                | 1.05 (0.81-1.36) | 0.72 (0.54-0.97) | 1.14 (0.79-1.65) |
| Triglycerides                           | 1.00                | 1.04 (0.80-1.35) | 0.72 (0.54-0.97) | 1.14 (0.79-1.65) |
| Diabetes                                | 1.00                | 1.00 (0.77-1.30) | 0.73 (0.54-0.98) | 1.18 (0.81-1.70) |
| Hypertension                            | 1.00                | 1.03 (0.80-1.34) | 0.72 (0.54-0.96) | 1.15 (0.79-1.66) |
| ABI                                      | 1.00                | 1.03 (0.79-1.33) | 0.72 (0.54-0.97) | 1.12 (0.79-1.62) |
| BMI                                      | 1.00                | 1.05 (0.81-1.36) | 0.72 (0.54-0.96) | 1.18 (0.82-1.71) |
| Visceral fat                            | 1.00                | 1.05 (0.81-1.36) | 0.72 (0.54-0.96) | 1.12 (0.78-1.62) |
| IL-6                                     | 1.00                | 1.02 (0.79-1.33) | 0.73 (0.54-0.98) | 1.06 (0.73-1.53) |
| CRP                                      | 1.00                | 1.04 (0.80-1.35) | 0.71 (0.53-0.95) | 1.10 (0.76-1.59) |
| Model 2 plus potential confounders†     | 1.00                | 1.00 (0.77-1.31) | 0.72 (0.54-0.97) | 1.20 (0.83-1.74) |
| Fully adjusted model‡                    | 1.00                | 0.98 (0.75-1.27) | 0.71 (0.53-0.96) | 1.05 (0.72-1.54) |

Abbreviations: ABI, ankle brachial index; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CHD, coronary heart disease; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; IL-6, interleukin 6; LDL-C, low-density lipoprotein cholesterol.

*Data are reported as hazard ratio (95% confidence interval).
†Cerebrovascular disease, cancer, hemoglobin A1c, and serum albumin.
‡Adjusted for age, sex, race, site, education, smoking status, physical activity, BMI, ABI, visceral fat, hypertension, diabetes, cerebrovascular disease, cancer, LDL-C, HDL-C, triglycerides, hemoglobin A1c, serum albumin, IL-6, and CRP.

Analyses stratified by sex showed that in men, light to moderate alcohol consumption appeared strongly associated with a decreased risk of both all-cause mortality (HR, 0.62; 95% CI, 0.43-0.90) and cardiac events (HR, 0.63; 95% CI, 0.43-0.92). Among women, light to moderate alcohol consumption was associated with a slightly nonsignificant cardiac event risk reduction (HR, 0.85; 95% CI, 0.52-1.36), and the risk of all-cause mortality was not affected.
However, the interaction between alcohol consumption and sex for all-cause mortality and cardiac events was not significant ($P > .10$ for interaction). We observed a significant interaction between alcohol consumption and race for all-cause mortality in men, with a stronger association between light to moderate alcohol consumption and death in black subjects (HR, 0.41; 95% CI, 0.22-0.77 vs HR, 0.82; 95% CI, 0.50-1.35 for white subjects) ($P = .007$ for interaction). Among women, moderate alcohol consumption was associated with a nonstatistically significant lower risk of cardiac events among black participants (HR, 0.60; 95% CI, 0.23-1.61), whereas among white participants, moderate alcohol consumption did not seem to affect the risk of cardiac events (HR, 1.07; 95% CI, 0.60-1.91) ($P = .04$ for interaction).

To better evaluate the impact of inflammation on the studied relationship, we performed further analyses stratified by levels of IL-6 and CRP (Figure 2). Among men with high levels of IL-6, light to moderate drinkers had a significantly lower risk of all-cause mortality (HR, 0.51; 95% CI, 0.33-0.81) and cardiac events (HR, 0.50; 95% CI, 0.30-0.83) compared with never and occasional drinkers. Conversely, among men with low levels of IL-6, light to moderate alcohol consumption was not associated with any appreciable risk reduction, and in these men, consumption of more than 7 drinks per week significantly increased all-cause mortality. The relationship between alcohol intake and health-related outcomes did not substantially differ in men with low or high levels of CRP. The interaction terms between alcohol consumption and inflammatory marker levels were not significant ($P > .10$).

The results of this study demonstrate that in well-functioning older adults, light to moderate alcohol consumption is associated with a 26% reduced risk of all-cause mortality and almost 30% reduced risk of cardiac events. The protective effect of light to moderate alcohol consumption was not mediated by its anti-inflammatory properties, but the largest protective effect of light to moderate alcohol consumption was observed among men with high levels of IL-6.

Despite the consistent findings of a number of studies that light to moderate alcohol intake is associated with reduced risk of CVD and death, controversies exist about the overall survival benefit of moderate alcohol consump-
In addition, some or all of the protective effect of light to moderate alcohol consumption on CVD might be attributed to unmeasured confounding. It has also been suggested that at least part of this relative protective effect may result from inclusion among nondrinkers of subjects who do not drink because of their poor health status (reverse causality). This issue may assume particular importance among older people. In fact, the proportion of individuals consuming alcohol decreases with age, a trend that has been related to worsening health over time.

In our study, relative to never/occasional drinking, light to moderate alcohol consumption was associated with a significantly reduced risk of cardiac events and with overall survival benefit. We simultaneously controlled for many potentially confounding variables, including social and lifestyle indicators and a number of established cardiovascular risk factors, and control strengthened rather than weakened the association. The potential issue of reverse causality was addressed by separating former drinkers from never drinkers and by exclusion of subjects with CHD or HF at baseline. Finally, our findings persisted in secondary analyses that excluded subjects abstaining from alcohol for health reasons.

To our knowledge, this is the first study with the specific aim to investigate the impact of inflammation on the relationship between alcohol consumption and health-related outcomes; only 1 recent study evaluated CRP as a potential mediator of this association. Light to moderate alcohol consumption is associated with lower levels of IL-6 and CRP, suggesting that the alcohol anti-inflammatory effect might be the link between light to moderate alcohol consumption and decreased risk of cardiovascular events. However, in the present study, the protective effect of light to moderate alcohol consumption was not mediated by its anti-inflammatory effect. The benefit of light to moderate alcohol consumption was mainly confined to men with high levels of IL-6, a strong predictor of cardiovascular events.

From this point of view, our results might support the hypothesis that individuals at increased risk of developing CVD might have the largest overall benefit of light to moderate alcohol consumption.

The mechanisms underlying the cardioprotective effect of light to moderate alcohol intake are complex and not completely understood. Recent findings highlight the importance of genetic factors and the cellular and molecular effects of ethanol. Although our findings confirm the association between alcohol intake and cardiovascular risk factors, the present study suggests that the protective effect of light to moderate alcohol consumption may not be mediated by its beneficial effects on lipids and inflammatory profile. These findings are consistent with those of Mukamal et al. who found no significant effect of potential mediators (including HDL-C and CRP) on the relationship between alcohol intake and CHD. Further studies are needed to explore this possibility and to clarify ethanol anti-inflammatory and molecular effects.

The present study has several limitations. Alcohol intake was assessed by a standardized self-reported questionnaire, which is prone to misreporting and misclassification. Nondifferential misclassification may have diluted the true association between alcohol intake and our outcomes. We were also unable to compare risks across types of alcoholic beverages. However, recent evidence suggests that the protective effect of alcohol intake is consistent across different types of beverages. Moreover, our study is based on a single alcohol intake assessment at 1 point in time. However, among older people, drinking patterns tend to be stable over time, and given the relatively short follow-up period, it is unlikely that intake varied substantially. Although the analysis considered a number of potential confounders, residual confounding effect cannot be completely ruled out because total independence from measured and unmeasured confounders cannot be established in observational studies. Finally, the small number of events may have affected our findings and limited our analyses, particularly for stratified analyses.

In conclusion, our findings provide evidence of a cardioprotective effect and survival benefit of light to moderate alcohol consumption among older people. The anti-inflammatory effect of moderate alcohol consumption does not seem to explain these beneficial effects. The net benefit of light to moderate alcohol consumption may vary as a function of sex, race, and background cardiovascular risk. From this point of view, recommendations on alcohol consumption should be based, as any medical advice, on a careful evaluation of an individual’s risks and benefits, in the context of adequate treatment and control of established cardiovascular risk factors.
REFERENCES