Published in final edited form as:
Am J Clin Nutr. 2007 August ; 86(2): 444–450.

Alcohol consumption, interleukin-6 and apolipoprotein E genotypes, and concentrations of interleukin-6 and serum amyloid P in older adults[1–3]

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Abstract

Background—Whether alcohol intake is associated with concentrations of interleukin-6 (IL-6) and serum amyloid P (SAP) is uncertain.

Objective—We determined how alcohol intake and apolipoprotein E (apo E) and IL-6 promoter (IL-6 -174G→C) polymorphisms interact for concentrations of IL-6 and SAP.

Design—In the Cardiovascular Health Study, 2454 older adults reported their intake of beer, wine, and liquor and underwent measurements of circulating IL-6 and SAP.

Results—Alcohol intake was not associated with IL-6 concentrations among apo E4-negative or IL-6C-positive participants but was positively associated among both apo E4-positive and IL-6C-negative participants (*P* for trend = 0.02 for both). The corresponding interactions on SAP were not significant for alcohol overall but were similar for liquor intake.

Conclusions—Among older adults free of clinical cardiovascular disease, specific IL-6 promoter and apo E alleles appeared to confer positive associations of alcohol consumption with IL-6 concentrations. Genetic heterogeneity should be considered in understanding the cardiovascular effects of alcohol intake.

Keywords

Alcohol; inflammatory markers; epidemiology

INTRODUCTION

Moderate alcohol consumption is associated with a lower risk of cardiovascular disease (CVD) in older adults than is abstention or heavy drinking (1). Recent evidence has suggested that this lower risk may be related to effects of alcohol use on inflammation. Both observational studies (2,3) and short-term clinical trials (4,5) suggest that C-reactive protein (CRP) concentrations are lower among moderate drinkers. In a previous analysis of inflammatory markers among

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The authors' responsibilities were as follows—NSJ, RPT, and DSS: data collection; KJM: data analysis; all authors: study design and writing or editing of the manuscript. None of the authors had a personal or financial conflict of interest.

2Supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health (contracts N01-HC-85079 through N01-HC-85086, N01-HC-35129, and N01 HC-15103) and the National Institute on Alcohol Abuse and Alcoholism (grant R21-AA-00499).

A full list of participating Cardiovascular Health Study investigators and institutions can be found at http://www.chs-nhlbi.org.

older adults enrolled in the Cardiovascular Health Study (CHS), alcohol intake was associated with lower concentrations of fibrinogen, white blood cell count, and factor VIII coagulant activity, but the relation of CRP was significantly modified by apolipoprotein E (apo E) genotype (6).

Limited data exist about the relation of alcohol use with other markers of inflammation and the possible modifying effects of specific genetic polymorphisms. High doses of ethanol in mice increase interleukin-6 (IL-6) concentrations in response (7). In observational studies, participants who consumed ≤1 drink/d tended to have the lowest concentrations of IL-6 (8,9). In another example of a gene-alcohol interaction on inflammatory markers (10), the Carotid Atherosclerosis Progression Study (CAPS) investigators found a U-shaped relation between alcohol use and IL-6 concentrations, but the relation was substantially modified by a well-described polymorphism in the IL-6 promoter (IL-6 -174G→C) known to influence IL-6 concentrations in CHS (11).

Serum amyloid P (SAP) is another well-characterized inflammatory marker. Like CRP, it is a pentraxin, a family of serum proteins characterized by 5 identical, noncovalently linked subunits. CRP and SAP are produced in the liver in response to inflammatory mediators such as IL-6; they regulate the classical complement pathway (12-14) and play key roles in clearance of autoantigens and host defense (15). No epidemiologic information exists on the association of SAP with alcohol use or its potential interaction with genes related to inflammation; in one cross-sectional study of 10 patients with alcoholism and 10 control subjects, SAP concentrations did not appear to differ between the 2 groups (16).

To further elucidate the possible proinflammatory or antiinflammatory effects of alcohol consumption, we evaluated the cross-sectional associations of alcohol use with IL-6 and SAP and their modification by apo E genotype and the IL-6 promoter polymorphism in the CHS, a population-based, longitudinal study of community-dwelling older adults (17).

SUBJECTS AND METHODS

Study population and design

The CHS is a prospective study of 5888 men and women aged ≥65 y who were randomly selected from Medicare-eligibility lists in 4 communities in the United States. Participants were not institutionalized or wheelchair dependent, did not require a proxy for consent, were not under treatment of cancer at the time of enrollment, and were expected to remain in their respective regions for ≥3 y. Participants (n = 5201) were recruited and examined in 1989 and 1990; in 1992 and 1993, an additional 687 black persons were recruited and examined.

Written informed consent was obtained from each participant. The institutional review board at each participating center approved the study.

The CHS study design and objectives were published previously (17). The baseline examination included standardized medical history questionnaires, physical examination, and blood collection. Follow-up contact occurred every 6 mo, alternating between telephone calls and clinic visits. Details of laboratory methods used in CHS were published previously (18).

Alcohol consumption

At the baseline visit and annually, participants separately reported their usual frequency of consumption of beer, wine, and liquor and the usual number of 12-ounce cans or bottles of beer (11-14 g/serving), 6-ounce glasses of wine (15-18 g/serving), and shots of liquor (14 g/serving) that they drank on each occasion. The full text of the CHS nutritional questionnaire is publicly available (19). At baseline, participants reported whether they had changed their

pattern of consumption during the previous 5 y and whether they had ever regularly consumed ≥5 drinks/d. Participants who reported abstention at baseline but responded yes to either of these questions were classified as former drinkers.

We categorized participants into categories according to weekly ethanol consumption as follows: long-term abstainer, former drinker, <1 drink (<12 g), 1-6 drinks (12-72 g), 7-13 drinks (84-156 g), and ≥14 drinks (≥168 g). For regression analyses, we used long-term abstainers as the reference category.

Inflammatory markers

A total of 2454 participants were included in a nested case-cohort study in the CHS (11); IL-6, SAP, or both were measured in the baseline blood samples of 2328 of these participants, who were included in our analyses. Details of blood collection; laboratory procedures; and measurements of lipids, CRP, fibrinogen, white blood cell count, and IL-6 in the CHS were described previously (6,18,20). SAP was measured with the use of an in-house enzyme-linked immunoabsorbent assay that uses a monoclonal antibody to human SAP (Cymbus Biotechnology, Chandlers Ford, United Kingdom) as the capture antibody, a rabbit polyclonal antibody to human SAP (Dako Corporation, Carpinteria, CA) as the primary detection antibody, and a horse-radish peroxidase-conjugated anti-rabbit antibody as the secondary detection antibody (Jackson Laboratories, West Grove, PA). Purified SAP for a standard was obtained from EMD Biosciences (Calbiochem, San Diego, CA). The analytic CV of this assay was 9%. The IL-6 assay had an analytic CV of 6.3% (20).

As in previous cross-sectional analyses of inflammatory factors (6), we excluded participants who were missing information on alcohol use (n = 10) or who had confirmed CVD at baseline [as previously defined (21,22)] (n = 625) to minimize the possibility that alcohol use or concentrations of inflammatory factors were altered after a clinical diagnosis. We then used sampling weights to account for the selection criteria and sampling strategy of the nested study, so that our results among the remaining 1693 participants reflect the entire CHS population.

Genotyping

We performed genotype testing of apo E and the IL-6 promoter as described (11,23). In brief, high-throughput genotyping with the use of microplate array diagonal gel electrophoresis was used to determine genotype at the -174 position of the IL-6 promoter (24,25). Apo E was genotyped with the use of a restriction isotyping method (26). Of the original 5865 CHS participants with information on baseline alcohol use, 275 declined consent for genetic testing for CVDs, and 378 were not successfully genotyped.

We dichotomized participants on the basis of each of the 2 genes. For apo E, the 3 major forms are distinguished by linked polymorphisms encoding amino acids at positions 112 and 158; the E4 isoform contains arginine at both positions. We categorized persons as apo E4 positive (ie, *E2/E4*, *E3/E4*, or *E4/E4*) or apo E4 negative (ie, *E2/E2*, *E2/E3*, or *E3/E3*); 308 of 365 apo E4-positive participants were *E3/E4*. For the IL-6 promoter polymorphism, we categorized participants as IL-6C positive (ie, *CC* or *CG*) or IL-6C negative (ie, *GG*).

Other covariates

We defined diabetes as a fasting blood glucose ≥ 126 mg/dL or the use of antidiabetic medication. We dichotomized educational attainment (completion of high school or less compared with at least some vocational school or college), income (<$16 000/y compared with ≥$16 000/y), and marital status (married compared with other). We assessed leisure-time physical activity as a weighted sum of kilocalories expended in specific physical activities (27). Height and weight were directly measured at the baseline visit. Participants self-reported

any history of arthritis. Depressive symptoms were ascertained with the use of the Centers for Epidemiologic Studies Depression scale (28). Medication use was assessed with the use of a validated inventory (29). Maximal internal and common carotid intima-media thicknesses (IMTs) were measured at baseline and standardized as previously described (30).

Statistical analysis

To account for the particular sampling frame used to generate the sample of CHS participants in the nested case-cohort study, we used appropriate sampling weights generated by the CHS Coordinating Center in all analyses. We examined the relations of alcohol consumption with inflammatory markers in adjusted models that included covariates of age, race, sex, education, income, marital status, depressive symptoms, body mass index [(BMI; in kg/m^2) as linear and quadratic terms], leisure-time energy expenditure (in kcal), current and former cigarette smoking, diabetes, arthritis, hormone replacement therapy use among women, (31) and aspirin and statin use. Additional adjustment for pack-years of smoking did not substantially change our results. SAP was generally reasonably symmetrically distributed and analyzed with the use of linear regression. Other inflammatory markers, including IL-6, were asymmetrically distributed and were analyzed with the use of linear regression after log transformation; the percentage of differences is presented accordingly.

In hypothesis-generating beverage-type analyses, we categorized the intake of each beverage as none, <1 drink/wk, 1-6 drinks/wk, or ≥7 drinks/wk. We then explored the relation of inflammatory variables with the intake of each beverage, separating former drinkers and simultaneously adjusting for the intake of the other 2 beverages (32).

We excluded former drinkers and treated the mean intake within categories as a continuous variable to test linear trend. We squared a centered linear trend variable to test quadratic trend but found no evidence of nonlinear relations. We tested the interaction of genotype with alcohol intake (as a linear term) and present stratified results when interaction appeared likely ($P < 0.10$). We have already presented the interactions of alcohol intake with apo E (but not IL-6) genotype for CRP, white blood cell count, fibrinogen (6), and carotid IMT (30), so we further examined their interaction with IL-6 genotype here. We used INTERCOOLED STATA for WINDOWS software (version 8.2; Stata Corporation, College Station, TX) to accommodate the sampling weights in all analyses.

RESULTS

The descriptive characteristics of the 1693 CHS participants with measurements of IL-6 and SAP, according to usual alcohol consumption, are shown in Table 1. Consistent with previous reports (30), heavier drinkers were more likely to be men (P for trend < 0.001), white (P for trend = 0.007), married (P for trend = 0.007), and current or former smokers (P for trend = 0.01). IL-6 and SAP were moderately correlated with each other (Pearson correlation coefficient: 0.30; $P < 0.001$). The Pearson coefficients for their correlations with CRP were 0.51 for IL-6 and 0.39 for SAP ($P < 0.001$ for both). Apo E and IL-6 genotypes were not associated ($P = 0.67$).

Alcohol consumption and IL-6

As seen in Table 1, neither IL-6 (P for trend = 0.75) nor SAP (P for trend = 0.32) was associated with alcohol intake in unadjusted, unstratified comparisons. No association of alcohol intake was observed with IL-6 after adjustment (Table 2).

Although apo E4 genotype was not itself associated with IL-6 concentrations ($P = 0.94$), we found a significant interaction between alcohol intake and apo E4 genotype for IL-6

concentrations ($P = 0.006$). As seen in Table 2, alcohol intake was not associated with IL-6 concentrations among apo E4-negative participants, but a positive association was observed among apo E4-positive participants, with 48% higher concentrations among the heaviest drinkers than among long-term abstainers. Differences in the association of alcohol and IL-6 were significant among the heaviest drinkers ($P = 0.01$) and nearly so among consumers of 1-6 drinks/wk (12-72 g) ($P = 0.07$).

IL-6 genotype was associated with IL-6 concentrations, being 9 ± 4% higher among IL-6C-positive participants (ie, participants with *CC* or *GC* genotypes). We also found a nearly significant interaction between alcohol intake and IL-6 genotype ($P = 0.06$), with a significant positive association of alcohol intake with IL-6 concentrations only among IL-6C-negative participants. The alcohol-IL-6 association was similar (and null) among IL-6C homozygotes and heterozygotes (data not shown). In the 156 apo E4-positive IL-6C-negative participants, IL-6 concentrations among the heaviest drinkers were 60 ± 44% higher than those among the long-term abstainers, which suggests that the 2 genes appeared to interact independently with alcohol intake.

Alcohol consumption and SAP

The adjusted relations of alcohol intake with SAP are also shown in Table 2. As with IL-6 concentrations, alcohol intake was not associated with SAP concentrations, nor was there an association with apo E4 genotype ($P = 0.77$). The linear interaction of alcohol intake with apo E genotype for SAP concentrations was not statistically significant ($P = 0.23$). SAP concentrations were 1.1 ± 0.7 mg/L higher among IL-6C-positive participants than among IL-6C-negative participants ($P = 0.11$). Parallel to our findings on apo E and SAP, the linear interaction term was not significant ($P = 0.21$).

Exploratory analyses of beverage type

We next explored the associations of inflammatory markers with consumption of either beer, wine, or liquor, after control for consumption of the other 2 beverages (Table 3). In general, the patterns of interaction with apo E and IL-6 genotypes paralleled the interactions seen for overall alcohol intake, most notably for the intake of liquor (the most heavily consumed beverage in CHS).

Beer consumption was not associated overall with concentrations of IL-6 and SAP. A positive relation of beer intake was observed with SAP concentrations among IL-6C-negative participants (P for trend = 0.03), but not among IL-6C-positive participants (P for interaction = 0.09).

Wine consumption was also not associated with concentrations of IL-6, but there was evidence for an interaction for SAP concentrations (P for interaction = 0.03), with a positive trend of wine intake with SAP among IL-6C-positive participants (P for trend = 0.09) but an inverse trend among IL-6C-negative participants (P for trend = 0.08).

No clear overall relations of liquor intake were observed with concentrations of IL-6 or SAP. However, the heaviest amount of liquor intake tended to be associated with higher IL-6 concentrations among apo E4-positive participants (P for interaction = 0.01) and with higher SAP concentrations among IL-6C—negative participants (P for interaction = 0.08).

Alcohol consumption, IL-6 genotype, and other inflammatory markers

Given that IL-6 genotype appeared to modify the association of heavier alcohol intake with concentrations of IL-6, we explored whether IL-6 genotype also influenced the associations of heavier intake with CRP, fibrinogen, and white blood cell count. IL-6C-positive participants

had 3 ± 1% higher concentrations of fibrinogen ($P = 0.06$), 14 ± 7% higher concentrations of CRP ($P = 0.04$), and 1 ± 2% higher white blood cell counts ($P = 0.56$). Formal tests of alcohol × genotype interaction were not significant in all 3 cases.

We also explored whether IL-6 genotype modified the association of alcohol use with carotid IMT as a measure of atherosclerosis. Although light alcohol intake was associated with lower IMT in the full CHS cohort (30), no amount of intake was associated with IMT in this smaller subcohort, and, correspondingly, no significant interaction of overall alcohol intake and genotype was observed.

DISCUSSION

In this analysis of older adults free of clinical CVD, there were significant positive relations of heavier alcohol intake with concentrations of IL-6 among both apo E4-positive and IL-6C-negative participants. The corresponding interactions on SAP concentrations were not statistically significant overall, but there were similar trends for liquor intake. These findings support the relevance of genetic heterogeneity in understanding the cardiovascular effects of alcohol consumption.

The relation of alcohol use with these markers of inflammation has not been extensively addressed. In the Health, Aging, and Body Composition Study, there was a J-shaped relation between alcohol use and IL-6, with the lowest concentrations among consumers of 1-7 drinks/wk (9). In 340 women enrolled in the Women's Health Study, Bermudez et al (8) also found a nonlinear relation, with the lowest IL-6 concentrations among those who consumed alcohol at least weekly but less than daily. The CAPS investigators found the lowest IL-6 concentrations among consumers of >15-30 g alcohol/d overall and among persons with *GG* and *GC* genotypes of the -174 polymorphism. However, among *CC* homozygotes, the relation was generally positive, with markedly higher concentrations associated with an intake of >45 g alcohol/d (ie, >3 drinks/d). It is not certain why our results for this gene × diet interaction appear to differ from those seen in CAPS, but our results were generally consistent for multiple different inflammatory markers. The effect of IL-6 genotype in the younger CAPS population was chiefly related to a magnitude of alcohol intake that was quite uncommon among older CHS participants.

We did not find an overall association of alcohol use with IL-6 in our analyses, despite the trends in other studies noted earlier. It is interesting that we also found little association of alcohol use with CRP in previous CHS analyses (6), again despite somewhat inverse findings in earlier studies (2,3). For both IL-6 and CRP, this may reflect better control of confounders, such as depressive symptoms and socioeconomic status, that were not included in previous studies or possibly different distributions of genetic variants that modify these associations (6).

In previous studies, we have found that apo E genotype modifies the association of alcohol use with carotid IMT (30) and risk of ischemic stroke and dementia (33,34) but not coronary heart disease (35). The parallel interactions of alcohol intake with apo E genotype for both inflammatory markers and cerebrovascular disease in CHS suggest that the apparent effect of alcohol use on inflammatory markers may have important causative consequences for older adults, particularly with respect to cerebrovascular disease. Furthermore, these interactions raise the possibility, if our findings are confirmed, that older adults should undergo routine apo E testing if they choose to drink alcohol.

SAP is an acute-phase reactant that correlates with concentrations of both CRP and IL-6 in CHS, although it may be best recognized for its link with Alzheimer disease. SAP is also a component of amyloid deposits including the cerebral amyloid characteristic of Alzheimer

disease (36), and its concentration in cerebrospinal fluid appears to predict the prevalence (37) and severity (38) of Alzheimer disease, although its causative role in that disease is as yet uncertain (39,40). It is interesting that IL-6 concentrations also may predict risk of dementia (41). In CHS, intake of 1-6 alcoholic drinks/wk was strongly associated with lower risk of incident Alzheimer disease, at least among apo E4-negative participants (34). This observation raises the possibility that the effects of alcohol intake on IL-6 and SAP concentrations among apo E4-positive participants that were seen in the present study could play a role in attenuating an otherwise beneficial effect of alcohol on cognitive function, perhaps mediated by changes in subclinical cerebrovascular disease (42).

We did not find strong evidence that beverage type substantially influenced concentrations of newer inflammatory markers in this study, which was similar to our previous findings on more conventional inflammatory markers (6). Of note, Estruch et al (4) found in their randomized trial that consumption of both wine and gin (≈2 drinks/d for 4 wk) lowered IL-1α concentrations, but only wine additionally lowered concentrations of CRP and adhesion molecules. Despite their preliminary nature, the results in the present study suggest that the modifying effect of IL-6 genotype on SAP may extend to all 3 beverage types.

The CHS has strengths but also limitations. As with any observational study, the associations we observed could be related, at least in part, to differences between drinkers and nondrinkers other than their amount of alcohol consumption, although we were able to adjust for a wide variety of demographic, socioeconomic, and clinical factors. We also separated former drinkers from longer-term abstainers, and our results typically showed dose-dependent relations.

We restricted our analyses to well-characterized polymorphisms in the apo E and IL-6 genes, for which strong prior data suggested interactions with alcohol use, thereby minimizing the possibility of false-positive associations. However, our findings may reflect interactions of alcohol with other polymorphisms in IL-6, apo E, or nearby genes that are in linkage disequilibrium with the variants we studied.

We relied on self-reported average alcohol consumption in this study, which has been validated in other epidemiologic investigations (43) and which is correlated with HDL cholesterol to the expected degree in the CHS. However, detailed data on drinking patterns were not available, so we could not distinguish between regular and episodic alcohol consumption, although binge-drinking rates decline with age and are likely to be low in this cohort study (44). Because CHS participants generally consumed limited amounts of individual alcoholic beverages, we also had limited power to determine how heavy alcohol consumption and beverage type relate to concentrations of inflammatory markers.

In conclusion, in this study of older adults, we found higher concentrations of IL-6 among the apo E4-positive and IL-6C-negative participants who were heavier alcohol drinkers. This interaction also tended to be similar for concentrations of SAP, at least for some beverage types. These results further support the possibility of genetic modulation of the health effects of alcohol and support further research into the potential risks of heavy alcohol consumption for genetically susceptible adults.

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TABLE 1

Characteristics of 1693 participants of the Cardiovascular Health Study (CHS) with inflammatory marker measurements, according to usual alcohol consumption[1]

	Alcohol consumption category[2]						
	None (*n* = 704)	**Former (*n* = 127)**	**<1 (<12) (*n* = 336)**	**1-6 (12-72) (*n* = 290)**	**7-13 (84-156) (*n* = 103)**	**≥14 (≥168) (*n* = 133)**	***P* for trend**
Alcohol consumption (drinks/wk)[3]	0	0	0.2	2.0	7.7	20.6	
Age (y)	72.8 ± 0.3[4]	72.3 ± 0.6	72.0 ± 0.4	72.0 ± 0.4	72.9 ± 0.7	71.4 ± 0.5	0.05
Female (%)	74	40	71	50	46	44	<0.001
Black (%)	22	23	10	11	6	8	0.007
Married (%)	63	65	69	75	82	78	0.007
Current smoker (%)	8	14	13	15	8	21	0.01
BMI (kg/m^2)[3]	27.3	27.4	26.9	26.1	25.5	26.2	0.02
Systolic blood pressure (mm Hg)	138 ± 1	139 ± 2	133 ± 1	131 ± 2	135 ± 3	138 ± 2	0.36
Diabetes (%)	19	24	9	11	9	9	0.07
Depressive symptom score	4.6 ± 0.2	4.8 ± 0.5	4.3 ± 0.3	3.6 ± 0.3	3.9 ± 0.5	4.2 ± 0.5	0.53
Energy spent in leisure-time physical activities (kcal)	1644 ± 128	1762 ± 257	2117 ± 176	2028 ± 163	1822 ± 226	1922 ± 227	0.69
Creatinine (mg/dL)	1.00 ± 0.01	1.08 ± 0.04	1.00 ± 0.02	1.02 ± 0.02	1.05 ± 0.03	1.03 ± 0.03	0.16
IL-6 (pg/mL)	2.4 ± 0.1	2.5 ± 0.3	2.2 ± 0.1	2.0 ± 0.1	2.1 ± 0.3	2.4 ± 0.2	0.75
SAP (mg/L)	31.3 ± 0.5	33.0 ± 1.2	30.7 ± 0.7	31.0 ± 0.7	31.1 ± 1.3	32.3 ± 1.1	0.32
Apo E4 positive	22	29	23	34	18	25	0.81
IL-6 - 174C positive	54	62	57	49	67	52	0.91

[1] IL-6, interleukin-6; Apo E4 positive indicates an apo E genotype of *E2/E4*, *E3/E4*, *E4/E4*. IL-6C positive indicates a genotype of *CC* or *GC*. SAP, serum amyloid *P*; apo E4, apolipoprotein E4. All characteristics were weighted to reflect the probability of sampling from the full CHS population. β values were derived from unadjusted tests of linear trend by using weighted linear or logistic regression and excluding former drinkers.

[2] Drinks/wk; g ethanol in parentheses.

[3] Mean.

[4] $\bar{x}$ ± = SE (all such values).

TABLE 2

Differences in interleukin-6 (IL-6) and serum amyloid P (SAP) among participants in the Cardiovascular Health Study (CHS) according to usual alcohol intake, relative to long-term abstainers[1]

	Alcohol consumption category[2]						
	None (*n* = 704)	**Former (*n* = 127)**	**<1 (<12) (*n* = 336)**	**1-6 (12-72) (*n* = 290)**	**7-13 (84-156) (*n* = 103)**	**≥14 (≥168) (*n* = 133)**	***P* for trend**
IL-6 (% difference)							
All participants	Ref	2 ± 9[3]	3 ± 5	-3 ± 5	-3 ± 9	7 ± 8	0.37
Apo E4 negative (*n* = 1143)	Ref	3 ± 12	4 ± 6	-7 ± 5	-6 ± 11	-3 ± 7	0.51
Apo E4 positive (n = 365)	Ref	13 ± 16	5 ± 9	13 ± 10	6 ± 16	48 ± 23	0.02
IL-6C negative (n = 675)	Ref	18 ± 18	1 ± 6	-1 ± 7	6 ± 22	27 ± 14	0.02
IL-6C positive (n = 850)	Ref	-2 ± 10	4 ± 7	1 ± 7	-6 ± 10	-3 ± 9	0.65
SAP (mg/L difference)							
All participants	Ref	-0.1 ± 1.4	0.2 ± 0.9	-0.1 ± 0.8	0.5 ± 1.3	1 ± 1.2	0.48

[1] Apo E4, apolipoprotein E4. Differences were derived from linear regression models adjusted for age, sex, race, current smoking, former smoking, marital status, education, income, leisure-time physical activity, BMI (linear and squared), depressive symptoms, arthritis, and diabetes and use of hormone replacement, aspirin, and statins, with weighting to reflect the probability of sampling from the full CHS population. Apo E4 positive indicates an apo E genotype of *E2/E4*, *E3/E4*, or *E4/E4*. IL-6C positive indicates a genotype of *CC* or *GC*. *P* values were derived from linear trend tests, excluding former drinkers. *P* values for interaction between alcohol use and genotype for IL-6 concentrations were 0.006 for apo E4 and 0.06 for IL-6C.

[2] Drinks/wk; g ethanol in parentheses.

[3] $\bar{x}$ ± SE (all such values).

TABLE 3

Differences in interleukin-6 (IL-6) and serum amyloid P (SAP) among participants in the Cardiovascular Health Study (CHS) according to usual intake of individual beverage types, relative to abstainers from each individual beverage[1]

	Alcohol consumption category[2]				
	None	<1 (<12)	1-6 (12-72)	≥7 (≥84)	*P* for trend
Beer (*n*)	1277	236	113	67	
IL-6 (% difference)	Ref	17 ± 7[3]	-2 ± 7	7 ± 9	0.89
SAP (mg/L difference)					
All participants	Ref	1.6 ± 1.1	1.2 ± 1.2	2.6 ± 1.7	0.26
IL-6C negative	Ref	0.4 ± 1.2	3.2 ± 1.8	5.0 ± 1.9	0.03
IL-6C positive	Ref	2.1 ± 1.6	-1.8 ± 1.8	0.4 ± 2.8	0.51
Wine (*n*)	1056	371	195	71	
IL-6 (% difference)	Ref	-13 ± 4	-12 ± 6	-14 ± 10	0.38
SAP (mg/L difference)					
All participants	Ref	-0.1 ± 0.8	0.3 ± 0.9	-0.3 ± 1.6	0.91
IL-6C negative	Ref	0.7 ± 1.2	0.6 ± 1.4	-3.4 ± 2.2	0.08
IL-6C positive	Ref	-0.2 ± 1.1	1.5 ± 1.4	3.4 ± 2.0	0.09
Liquor (*n*)	1151	261	150	131	
IL-6 (% difference)					
All participants	Ref	2 ± 6	0.2 ± 7	7 ± 8	0.42
Apo E4 negative	Ref	4 ± 7	-1 ± 8	-6 ± 8	0.23
Apo E4 positive	Ref	0.1 ± 11	-5 ± 12	37 ± 21	0.03
SAP (mg/L difference)					
All participants	Ref	-1.1 ± 0.9	-1.7 ± 1.0	0.2 ± 1.0	0.69
IL-6C negative	Ref	-1.0 ± 1.3	-2.1 ± 1.5	2.5 ± 1.6	0.08
IL-6C positive	Ref	-1.8 ± 1.2	-1.6 ± 1.5	-1.7 ± 1.4	0.28

[1] Apo E4, apolipoprotein E4. Differences were derived from linear regression models adjusted for age, sex, race, current smoking, former smoking, marital status, education, income, leisure-time physical activity, BMI (linear and squared), depressive symptoms, arthritis, and diabetes; use of hormone replacement, aspirin, and statins; and intake of the other 2 beverage types, with weighting to reflect the probability of sampling from the full CHS population. Apo E4 positive indicates an apo E genotype of *E2/E4*, *E3/E4*, or *E4/E4*. IL-6C positive indicates a genotype of *CC* or *GC*. *P* values for trend exclude former drinkers. *P* values for the interactions of beer, wine, and liquor with genotype for IL-6 concentrations were 0.97, 0.40, and 0.01 for apo E4 and 0.62, 0.96, and 0.27 for IL-6C. The corresponding *P* values for interaction for SAP concentrations were 0.71, 0.14, and 0.97 for apo E4 and 0.09, 0.03, and 0.08 for IL-6C.

[2] Drinks/wk; g ethanol in parentheses.

[3] $\bar{x}$ ± SE (all such values).