A Prospective Study of the Health Effects of Alcohol Consumption in Middle-Aged and Elderly Men

The Honolulu Heart Program

Robert J. Goldberg, PhD; Cecil M. Burchfiel, PhD; Dwayne Reed, MD; Gilbert Wergowske, MD; Darryl Chiu, MS

Background The study objective was to determine the association between reported alcohol consumption and total mortality, mortality from selected causes, and incident nonfatal chronic disease events in middle-aged (51 to 64 years old) and elderly (65 to 75 years old) men during an approximately 15-year follow-up period.

Methods and Results We conducted a prospective epidemiological study of Japanese-American men who were participating in the Honolulu Heart Program and were free from coronary heart disease, cerebrovascular disease, and cancer at baseline examination and at subsequent reexamination 6 years later. Self-reported alcohol consumption was determined twice: at the baseline examination in 1965 through 1968 and at reexamination approximately 6 years later (1971 through 1974). Four primary alcohol consumption groups who reported similar alcohol intake at the time of these two clinical examinations were considered: abstainers and light (1 to 14 mL of alcohol per day), moderate (15 to 39 mL of alcohol per day), and heavy (≥40 mL of alcohol per day) drinkers. Study end points were also determined in very light (1 to 4.9 mL of alcohol per day) drinkers and in men who reported a change in their alcohol intake between examinations. Longitudinal follow-up was carried out through the end of 1988 with determination of selected fatal and nonfatal events according to alcohol intake. After controlling for several potentially confounding factors, total mortality exhibited a J-shaped pattern in relation to alcohol consumption in middle-aged and elderly men. There was a trend for lower rates of occurrence of combined fatal and nonfatal coronary heart disease events with increasing alcohol consumption in both middle-aged and elderly men. Increasing alcohol consumption was related to an increased risk of fatal and nonfatal strokes in middle-aged men, whereas elderly light and moderate drinkers were at increased risk for fatal and nonfatal strokes. Heavy drinkers were at increased risk for fatal and nonfatal malignant neoplasms in the two age groups examined.

Conclusions The results of this long-term prospective study provide a balanced perspective of the health effects of alcohol consumption in middle-aged and elderly men. High levels of alcohol consumption were shown to be related to an increasing risk of diseases of considerable public health importance. These findings suggest that caution be taken in formulating population-wide recommendations for increases in the population levels of alcohol consumed given the associated significant social and biological problems of high consumption levels. (Circulation. 1994;89:651-659.)

Key Words • alcohol • age • mortality • morbidity

A number of studies in men and women have suggested that consumption of a moderate amount of alcohol is associated with a reduced risk of coronary heart disease. On the other hand, several studies have shown that both nondrinkers and heavy drinkers of alcohol have increased mortality rates from all causes of death as well as from cardiovascular disease in particular. Several biologically plausible mechanisms are thought to mediate the apparent beneficial effects of alcohol on coronary heart disease, including favorable effects on levels of high-density lipoprotein cholesterol, hemostatic parameters, and possibly other factors. Methodological questions have been raised, however, as some studies have included ex-drinkers and lifelong abstainers in the nondrinker comparison group as well as those with prior chronic disease. Thus, questions remain unanswered as to the long-term impact of alcohol consumption on total as well as cause-specific mortality. In addition, there are limited data concerning the relation of alcohol and changes in alcohol consumption over time to incident chronic disease end points as well as the effects of alcohol consumption in the middle-aged compared with the elderly. Given the significant social and behavioral consequences of alcohol use, it remains of considerable public health importance to examine the overall health effects of alcohol consumption.

The purpose of the present study was to extend previous findings from the Honolulu Heart Program concerning the overall health effects of alcohol consumption measured at two distinct points in time on total mortality as well as cause-specific morbidity and mortality over an approximate 15-year follow-up period, with a specific focus on the comparison of health outcomes in the elderly with those in the middle-aged.

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From the Honolulu Heart Program (G.W., D.C.), Honolulu, Hawaii; the Honolulu Epidemiology Research Section (C.M.B., D.W.R.), Epidemiology and Biometry Program, National Heart, Lung, and Blood Institute, Honolulu, Hawaii, and Bethesda, Md; and the Department of Medicine (R.J.G.), University of Massachusetts Medical School, Worcester.

Reprint requests to C.M. Burchfiel, PhD, Honolulu Heart Program, Kuakiki Medical Center, 347 North Kuakini St, Honolulu, HI 96817.
The intent of this prospective epidemiological study was to provide a balanced perspective for public policy recommendations concerning the health benefits or risks associated with alcohol ingestion.

**Methods**

The Honolulu Heart Program originated as a prospective study of coronary heart disease and stroke among a cohort of 8006 men of Japanese ancestry born between 1900 and 1919 and residing on the Hawaiian island of Oahu in 1965. Details of the selection of the cohort, study design, and methods of examination have been described previously.\(^{24-29}\) Information collected from the baseline examination of these men between 1965 and 1968 consisted of various demographic, medical history, and sociocultural factors, including blood pressure, serum cholesterol levels, cigarette smoking, dietary habits, and alcohol consumption. Between 1971 and 1974, a third examination of the remaining cohort members was conducted in which a detailed clinical history and assessment of changes in various cardiovascular disease risk factors, including alcohol consumption, were carried out. Information concerning additional coronary risk factors, lifestyle characteristics, and diet have been described previously.\(^{27-31}\)

To minimize misclassification of alcohol intake, consumption of alcohol was based on information obtained from the baseline examination and the subsequent reexamination 6 years later. Usual alcohol intake, as determined through a series of questions asked by trained interviewers at the time of examinations 1 and 3, is expressed in milliliters per day of ethanol using standard conversion factors for beer, wine, and liquor; beer was considered to be 3.7% ethanol; wine, 10%; and liquor, 38%.\(^{30}\)

In the middle-aged and elderly population sample under study, approximately 31% of those consuming alcohol reported consuming beer only, 9% consumed hard liquor or spirits only, and 1% consumed wine only; approximately 38% consumed beer and liquor, and 16% reported consuming all three types of alcoholic beverages.

Abstainers from alcohol were defined as those men who did not report consuming any alcohol at the time of the baseline examination as well as at the subsequent reexamination. Light, moderate, and heavy alcohol consumers were defined as those who consistently reported consuming 1 to 14 mL of alcohol per day, 15 to 39 mL of alcohol per day, and ≥40 mL of alcohol per day, respectively, at each of these examinations. In addition to these four primary comparison groups of men who had maintained their alcohol habits at the time of the two clinical examinations, analyses were carried out in men who reported a change in their alcohol consumption patterns between these two cohort examinations. For this analysis, three groups were examined: those who had abstained from alcohol at examination 1 and reported their alcohol intake as light or moderate at the time of examination 3, those who reported their intake as light or moderate at the baseline examination and were subsequently classified as heavy drinkers at examination 3, and those who were classified as heavy drinkers at the baseline examination and subsequently reported a reduction in their alcohol intake at the time of examination 3 either to complete abstention or to light or moderate drinking.

Deaths and major nonfatal chronic disease events among men in this cohort were determined through ongoing review of death certificates, obituary notices, and monitoring of hospital discharges as part of the routine surveillance activities of this prospective study. For each death identified, an underlying cause (independent of the cause appearing on the death certificate) was determined by a panel of study physicians on the basis of all available information. All available evidence, including examination findings and autopsy information, was considered in assigning cause of death with eventual classification according to the eighth revision of *International Classification of Disease* (ICD) coding. ICD classifications were used for deaths attributed to coronary heart disease (ICD codes 410-414), cerebrovascular disease (ICD codes 430-438), and malignant neoplasms (ICD codes 140-239). Deaths from all remaining causes of death were also examined in relation to age and alcohol consumption. In terms of incident cardiovascular or cancer events, these end points were determined through routine hospital surveillance activities, with standardized definitions used for the classification of these events.\(^{27-31}\)

The period of follow-up began from the third examination (1971 through 1974) through the end of 1988.

**Data Analysis**

ANOVA and \(x^2\) test for trends were used to examine differences in selected continuous and categorical variables in the alcohol comparison groups stratified according to age. Age-adjusted morbidity and mortality rates (per 1000 population) were calculated to examine differences in the incidence rates of selected fatal and nonfatal end points (separately for middle-aged [51 to 64 years old] and elderly [65 to 75 years old] men) according to alcohol intake. Because of the instability of estimated rates based on small numbers of events, incidence rates of morbidity or mortal end points are not reported when the number of events was two or less. Person-years of follow-up were also used to adjust for varying lengths of follow-up and yielded similar results in the middle-aged and elderly. Age adjustment was carried out by the direct method using the age structure of the entire population at risk. Age was calculated at the time of the third clinical examination between 1971 and 1974. A proportional-hazards multivariable regression approach was used to examine the association of alcohol consumption (separately in middle-aged and elderly men) with pooled fatal and nonfatal events of coronary heart disease, cerebrovascular disease, and cancer while controlling for differences in potentially confounding factors. For multiple events of the same type, only the initial event was included; individuals who had more than one type of event (eg, stroke, myocardial infarction) were included for both outcomes. Linear and quadratic multivariate-adjusted relations between alcohol intake and the principal study end points were also modeled with alcohol as a continuous variable.

**Results**

A total of 6069 men without evidence of coronary heart disease, cerebrovascular disease, or cancer at the time of the third cohort examination (1971 through 1974) comprised the study population. Among the 2946 middle-aged men who reported their alcohol intake to have essentially remained the same at the time of both examination 1 and examination 3, 1052 (36%) were classified as having abstained from alcohol at both examinations, 1313 (44%) were considered light drinkers (1 to 14 mL of alcohol per day) at both of these examinations, 265 (9%) were considered moderate drinkers (15 to 39 mL of alcohol per day), and 316 (11%) were considered heavy drinkers (≥40 mL of alcohol per day). In the 847 elderly men who reported their usual alcohol intake to be stable at the time of examinations 1 and 3, 381 (45%) had abstained from alcohol at both examinations, 324 (38%) were classified as light drinkers at both examinations, 70 (8%) were classified as moderate drinkers, and 72 (9%) were classified as heavy drinkers. In addition to these principal comparison groups, to assess the health effects of changes in reported alcohol intake between the two clinical examinations, three subgroups were examined: 550 middle-aged and 146 elderly men who reported a change in their usual alcohol intake from abstinence at examination 1 to light or moderate drinking at exami-
nation 3, 260 middle-aged and 52 elderly men who changed from light or moderate drinking at examination 1 to heavy drinking at examination 3, and 264 middle-aged and 66 elderly men who reported a reduction in their alcohol intake from heavy drinking at the baseline examination to either abstinence or light or moderate drinking at examination 3.

Differences in various lifestyle, physiological, and dietary characteristics in the four primary comparison groups were examined separately in middle-aged and elderly men (Table 1). The data suggest trends for significantly increasing systolic blood pressure with increasing levels of reported alcohol intake in middle-aged men, lower total serum cholesterol levels with increasing alcohol consumption in both age groups, and progressively higher triglyceride levels with increasing alcohol intake in middle-aged men. Serum glucose and uric acid levels increased with increasing levels of alcohol consumed. Significant differences in body mass, hematocrit, index of physical activity, and vital capacity according to reported alcohol intake were also seen. In both age groups examined, the proportion of current cigarette smokers and regular coffee drinkers increased with increasing levels of alcohol consumed. In both middle-aged and elderly men, significant differences were seen in total caloric intake and percentage of calories from selected dietary factors according to alcohol intake; these latter data excluded the contribution of alcohol to these dietary measures.

The relation of alcohol consumption to age-adjusted total and cause-specific mortality rates is shown for middle-aged and elderly men (Table 2). Total mortality rates exhibited a J-shaped curve in relation to alcohol consumption in middle-aged and elderly men. In terms of mortality attributed to coronary heart disease, the lowest death rates among middle-aged men were seen among light and heavy drinkers, whereas the lowest coronary heart disease death rates in the elderly were seen in those consuming moderate amounts of alcohol. A progressive increase in the age-adjusted rates of death from cerebrovascular disease with increasing levels of alcohol consumption was seen in middle-aged men, and a relatively similar pattern was seen in the elderly. Appropriate caution needs to be exercised in the interpretation of the coronary heart disease and cerebrovascular disease mortality findings because a relatively small number of these events occurred, particularly among moderate and heavy drinkers in the two age strata examined. Death rates from all malignant neoplasms exhibited a J-shaped curve in relation to alcohol intake in middle-aged and elderly men. In middle-aged men, there was an increase in deaths from all other causes of death among those consuming the heaviest amounts of alcohol, whereas elderly moderate drinkers were at greatest risk of dying from all other causes of death.

A total of 409 men died between the time of the baseline examination and reexamination approximately 6 years later. Because the present classification schema for alcohol consumption required men to have survived to the third clinical examination, a separate analysis was carried out among men classified according to alcohol consumption at the time of the baseline examination. Persons with coronary heart disease, cerebrovascular disease, or cancer at the time of the initial examination were excluded from further consideration. The results of this analysis confirmed the J-shaped all-cause mortality pattern previously observed: age-adjusted total mortality rates (per 1000) across the two age strata examined were 52.6, 46.8, 50.7, and 81.7 for abstainers and light, moderate, and heavy drinkers, respectively.

The overall effects of alcohol intake on health-related outcomes in this cohort are shown in the Figure. The occurrence of deaths from all causes and the incidence of combined fatal and nonfatal events of coronary disease, cerebrovascular disease, and cancer were analyzed separately in middle-aged and elderly men. These results revealed a slight to no beneficial effect of light alcohol intake on total mortality, cerebrovascular disease, and cancer in middle-aged men, whereas elderly moderate drinkers were at reduced risk for all-cause mortality and the coronary heart disease end points examined. With the exception of the beneficial effects of heavy reported alcohol ingestion on coronary heart disease in middle-aged men, heavy drinkers were at greatest risk for the majority of the combined end points examined.

Because of the often observed association between alcohol consumption and cigarette smoking, we carried out a separate analysis of the relation between alcohol intake and the principal study outcomes while adjusting for age and smoking status. Associations similar to those previously observed were seen for all-cause mortality and fatal and nonfatal events of coronary disease, cerebrovascular disease, and cancer as these trends were not materially affected after controlling for age and smoking status. For example, among middle-aged men, the age- and smoking-adjusted all-cause mortality rates were 153.4, 136.0, 202.5, and 277.6 in abstainers and light, moderate, and heavy drinkers, respectively. In the elderly, the age- and smoking-adjusted all-cause mortality rates were 396.4, 388.8, 359.7, and 465.1 in similar comparison groups, respectively.

The association of alcohol consumption to combined fatal and nonfatal events in this cohort was examined through the use of a proportional-hazards regression analysis in which age, systolic blood pressure, serum cholesterol, serum triglycerides, cigarette smoking, coffee consumption, uric acid, and caloric consumption were simultaneously controlled for (Table 3). In middle-aged men, there were trends for increasing alcohol consumption to be related to an increased risk of all-cause mortality in a J-shaped pattern and to cerebrovascular disease and cancer in a direct relation. An inverse dose-response association was seen between alcohol consumption and fatal and nonfatal coronary disease events. In the elderly, moderate alcohol ingestion was associated with decreased all-cause mortality, and increased alcohol intake was negatively associated with coronary heart disease. Light and moderate drinkers were at increased risk for cerebrovascular disease, whereas heavy drinkers were at the greatest risk of developing fatal or nonfatal cancer events.

Because of discrepant findings in the literature with regard to the association between alcohol intake and hemorrhagic (positive) or ischemic (inverse) strokes, we carried out a separate analysis of the association between alcohol consumption and pooled fatal and nonfatal strokes. Among middle-aged men, relative to abstainers, the multivariable-adjusted risk of developing a
### Table 1. Mean Levels and Percent Distribution of Selected Lifestyle, Physiological, and Dietary Characteristics According to Alcohol Consumption and Age: Honolulu Heart Program

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Middle-Aged Men (51 to 64 years old)</th>
<th>Elderly Men (65 to 75 years old)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Abstainer (n=1052)</td>
<td>Light Drinker (n=1313)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>129.6 129.4 131.7 135.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total serum cholesterol, mg/dL</td>
<td>221.2 219.2 218.8 209.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Serum triglycerides, mg/dL</td>
<td>223.5 233.6 250.2 281.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Serum glucose, mg/dL†</td>
<td>156.7 152.2 156.7 160.9</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Serum uric acid, mg/dL</td>
<td>5.7 5.9 6.4 6.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.1 24.2 23.9 23.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>44.8 44.7 45.1 45.1</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Physical activity index</td>
<td>33.0 32.6 32.9 33.2</td>
<td>NS</td>
</tr>
<tr>
<td>Forced expiratory volume, L/m²</td>
<td>1.03 1.07 1.07 1.03</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cigarette smoking, %</td>
<td>35.7 42.3 49.4 72.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>22.2 25.2 30.9 18.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Regularly drink coffee on a daily basis, %</td>
<td>78.7 86.9 86.8 82.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diet</td>
<td>Total calories 2306 2341 2241 2166</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Calories, %</td>
<td>Carbohydrates 48.7 46.6 46.7 47.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Protein 16.8 17.3 17.7 17.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Total fat 34.5 36.1 35.7 34.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Polyunsaturated fat 6.1 6.4 6.5 6.6</td>
<td>&lt;.025</td>
</tr>
<tr>
<td></td>
<td>Monounsaturated fat 13.2 13.8 13.6 12.9</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*One-way ANOVA for continuous variables and χ² test for categorical variables.
†Nonfasting sample taken 1 hour after a 50-g glucose load.
‡In 1 second corrected for height.

Fatal or nonfatal thromboembolic stroke was 0.84, 1.44, and 0.66 for light, moderate, and heavy drinkers, respectively; these multivariable-adjusted risks for thromboembolic stroke were 1.12, 1.64, and 0.70 in the elderly for the respective alcohol comparison groups. In terms of the multivariable-adjusted risk for fatal or nonfatal hemorrhagic strokes, the adjusted risk for development of this end point was 4.02, 1.86, and 4.59 for light, moderate, and heavy drinkers, respectively, among middle-aged men and 1.70, 0.01, and 3.86 for similar comparison groups in the elderly. These latter findings need to be interpreted cautiously given the small number of hemorrhagic strokes occurring in middle-aged (n=30) and elderly (n=11) men.

Linear and quadratic terms for alcohol intake were added to the proportional-hazards regression models to examine further the independence of the relation of alcohol consumption with total mortality and pooled fatal and nonfatal events of coronary heart disease, cancer, and cerebrovascular disease separately in middle-aged and elderly men. The results of this analysis showed a significant quadratic curvilinear relation between alcohol intake and combined coronary heart disease events (P<.025) and a linear relation of borderline statistical significance (P=.06) between alcohol consumption and fatal and nonfatal cancers. These associations were seen only in middle-aged men. None of the examined end points were significantly associated with alcohol intake in elderly men in either a linear or a quadratic direction.

An additional analysis was carried out to examine the consistency of the observed findings while eliminating from consideration a variety of conditions that may be related to several of the end points examined and to changes in an individual's alcohol intake. For this analysis, men with a gastrectomy, liver disease, colon or rectal disease, pancreatic disease, gout, or significant weight loss (>10 kg) occurring between examinations 1
TABLE 2. Age-Adjusted Mortality Rates (per 1000) From All Causes and Selected Causes of Death According to Alcohol Consumption and Age: Honolulu Heart Program

<table>
<thead>
<tr>
<th>Alcohol Consumption</th>
<th>Men</th>
<th>Total</th>
<th>Coronary Heart Disease</th>
<th>Cerebrovascular Disease</th>
<th>Cancer</th>
<th>All Other Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Middle-aged (51 to 64 years old)</td>
<td>Abstainer</td>
<td>1052</td>
<td>154.2 (167)</td>
<td>32.4 (35)</td>
<td>7.8 (8)</td>
<td>67.4 (73)</td>
</tr>
<tr>
<td></td>
<td>Light Drinker</td>
<td>1313</td>
<td>136.8 (176)</td>
<td>24.3 (31)</td>
<td>10.8 (14)</td>
<td>54.4 (70)</td>
</tr>
<tr>
<td></td>
<td>Moderate Drinker</td>
<td>265</td>
<td>199.8 (52)</td>
<td>46.7 (12)</td>
<td>20.1 (5)</td>
<td>95.6 (25)</td>
</tr>
<tr>
<td></td>
<td>Heavy Drinker</td>
<td>316</td>
<td>275.6 (86)</td>
<td>22.5 (7)</td>
<td>31.5 (10)</td>
<td>134.7 (42)</td>
</tr>
<tr>
<td>Elderly (65 to 75 years old)</td>
<td>Abstainer</td>
<td>381</td>
<td>394.2 (153)</td>
<td>55.1 (22)</td>
<td>32.9 (13)</td>
<td>143.5 (55)</td>
</tr>
<tr>
<td></td>
<td>Light Drinker</td>
<td>324</td>
<td>388.7 (125)</td>
<td>59.9 (19)</td>
<td>46.1 (15)</td>
<td>129.5 (42)</td>
</tr>
<tr>
<td></td>
<td>Moderate Drinker</td>
<td>70</td>
<td>364.2 (25)</td>
<td>* (2)</td>
<td>* (1)</td>
<td>116.1 (8)</td>
</tr>
<tr>
<td></td>
<td>Heavy Drinker</td>
<td>72</td>
<td>511.8 (35)</td>
<td>47.6 (4)</td>
<td>57.1 (4)</td>
<td>214.2 (14)</td>
</tr>
</tbody>
</table>

Numbers in parentheses refer to the number of men developing specific endpoints.
* Rates not reported due to the small number of events.

and 3 and those who died within 1 year of examination 3 were excluded, as were those who had been previously excluded because of a diagnosis of coronary disease, cerebrovascular disease, or cancer at or before examination 3. This resulted in an available sample of 3051 individuals, 2344 of whom were middle-aged and 707 of whom were elderly. These exclusions did not alter the results seen previously. Although not presented, age-adjusted total mortality rates and death rates from coronary heart disease were lowest in light drinkers, whereas the death rates from cerebrovascular disease and cancer were highest in heavy drinkers. Essentially similar mortality trends were seen in middle-aged and elderly men.

The incidence rates of the various fatal and nonfatal end points were examined in those consuming small amounts of alcohol (1 to 4.9 mL of alcohol per day) at the time of both examinations (separately in the middle-aged and elderly). In general, the rates for the very light drinkers were similar to those seen for men classified as light drinkers at both examinations.

Finally, the age-adjusted mortality rates from all causes and selected causes of death and nonfatal events in middle-aged and elderly men were examined separately for those who had changed their alcohol intake during the 6-year interval between examinations (Table 4). Heavy drinkers who had reduced their alcohol consumption over time remained at an increased risk of dying from all causes of death and from fatal and nonfatal cerebrovascular events. In general and regardless of age, the morbidity and mortality experience of

**Overall effects of alcohol intake on health-related outcomes in this cohort.**
those who were classified as abstainers from alcohol at examination 1 but as light or moderate drinkers at subsequent reexamination was similar to that of men who were classified as light or moderate drinkers at both examinations, although these trends were less apparent in elderly men.

A proportional-hazards regression analysis was carried out to examine the association between changes in alcohol consumption between the two clinic examinations and selected study outcomes while controlling for previously described characteristics. The results of this analysis are shown in Table 5, with somewhat divergent trends seen in middle-aged and elderly men between reported change in alcohol intake and several of the end points examined.

**Discussion**

A variety of longitudinal studies carried out in diverse population settings have examined the relation between alcohol consumption and mortality from all causes and from coronary heart disease in particular. These studies have included middle-aged men residing in the United Kingdom, Puerto Rico, Yugoslavia, Great Britain, Eastern Finland, Albany, NY, and Framingham, Massachusetts; men and women enrolled in the Kaiser-Permanente prepaid health plan; those living in Australia and middle-aged male employees of the Chicago Western Electric and Peoples Gas companies. More recent reports have examined the association of alcohol ingestion and various chronic disease end points and mortality in residents of Alameda County, Calif, who are 35 years old or older; in middle-aged women enrolled in the Nurses’ Health Study; in men 40 to 59 years old participating in the American Cancer Society Prospective Study; in middle-aged to elderly men enrolled in the Health Professionals Follow-up Study; and in middle-aged men from the two rural cohorts of the Seven Countries Study. Extensive reviews of the possible causal relation and mechanisms between alcohol and atherosclerosis and of the studies examining the association of alcohol consumption to total mortality, cardiovascular morbidity and mortality, and other disease end points have also been carried out.

Since the original observation of a U-shaped relation between alcohol ingestion and total mortality, the weight of epidemiological evidence has suggested a beneficial effect of light and moderate drinking on health effects in general and on coronary heart disease in particular; nondrinkers and those consuming heavy amounts of alcohol appear to have higher total and cardiovascular disease mortality rates. Recent examination of this important and controversial public health topic, however, has questioned the potentially protective role of low-to-moderate amounts of alcohol because of the possible misclassification of those abstaining from alcohol and the possibilities of an inverse linear association between alcohol consumption and selected health outcomes as opposed to the widely promulgated U- or J-shaped curve.

The results of the present longitudinal study extend previous observations from the Honolulu Heart Program. The initial report from this study suggested a strong negative association between consumption of alcohol and 6-year incidence rates of fatal and nonfatal episodes of coronary disease, with the lowest incidence rates seen in moderate drinkers and the highest incidence rates seen in nondrinkers. In the follow-up study to this original observation was observed a U-shaped curve in relation to baseline alcohol consumption and total mortality over an 8-year follow-up period, an inverse relation between mortality from coronary heart disease and intake of alcohol, and a positive association between alcohol ingestion and deaths from cancer, stroke, and cirrhosis of the liver.

The strengths of the present observational study include a large and well-described cohort of middle-aged and elderly Japanese men followed over a long period of time (15 years) with high rates of successful follow-up and identification and classification of disease end points according to predefined criteria, classification of exposure to alcohol at two distinct points in time to minimize misclassification of this primary exposure factor, and use of multivariate regression techniques to examine the relation between reported alcohol intake and various fatal and nonfatal events while controlling for other covariates that might ex-
TABLE 4. Age-Adjusted Incidence Rates (per 1000) of Combined Fatal and Nonfatal Events According to Changes in Alcohol Consumption and Age: Honolulu Heart Program

<table>
<thead>
<tr>
<th>Men</th>
<th>Change in Alcohol Intake Between Examinations 1 and 3</th>
<th>n</th>
<th>Total Mortality</th>
<th>Coronary Heart Disease Events</th>
<th>Cerebrovascular Disease Events</th>
<th>Cancer Events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Abstainer to light/moderate drinker</td>
<td>550</td>
<td>168.5 (93)</td>
<td>165.4 (64)</td>
<td>45.1 (25)</td>
<td>211.6 (117)</td>
</tr>
<tr>
<td></td>
<td>Light/moderate drinker to heavy drinker</td>
<td>260</td>
<td>171.5 (45)</td>
<td>79.8 (9)</td>
<td>53.1 (14)</td>
<td>295.8 (78)</td>
</tr>
<tr>
<td></td>
<td>Heavy drinker to abstainer/light/moderate drinker</td>
<td>264</td>
<td>260.3 (68)</td>
<td>151.9 (28)</td>
<td>74.7 (19)</td>
<td>294.5 (88)</td>
</tr>
<tr>
<td>Elderly (65 to 75 years old)</td>
<td>Abstainer to light/moderate drinker</td>
<td>146</td>
<td>353.4 (51)</td>
<td>211.3 (28)</td>
<td>134.5 (20)</td>
<td>244.6 (35)</td>
</tr>
<tr>
<td></td>
<td>Light/moderate drinker to heavy drinker</td>
<td>52</td>
<td>423.7 (22)</td>
<td>161.0 (8)</td>
<td>* (1)</td>
<td>398.3 (21)</td>
</tr>
<tr>
<td></td>
<td>Heavy drinker to abstainer/light/moderate drinker</td>
<td>66</td>
<td>440.6 (30)</td>
<td>* (1)</td>
<td>229.5 (15)</td>
<td>347.6 (22)</td>
</tr>
</tbody>
</table>

Numbers in parentheses refer to the number of men developing specific end points. *Rates not reported due to the small number of events.

plain or confound the observed association. The exclusion of men with conditions that might have accounted for the observed findings lends further credence to the study results. The present study also provides insights into the possible extent of misclassifica-

fication of alcohol consumption by use of a single measurement. Although still not necessarily a valid indicator of actual amount of alcohol consumed and possibly because of the categorical cutoff points selected for determination of the various alcohol con-

TABLE 5. Multivariable*-Adjusted Relative Risks of Combined Fatal and Nonfatal Events Associated With Changes in Alcohol Consumption and Age: Honolulu Heart Program

<table>
<thead>
<tr>
<th>Alcohol Consumption</th>
<th>Middle-Aged Men (51 to 64 years old)</th>
<th>Elderly Men (65 to 75 years old)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Mortality</td>
<td>Coronary Heart Disease Events</td>
</tr>
<tr>
<td>Abstainer from alcohol at examinations 1 and 3†</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Change in alcohol intake between examinations 1 and 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstainer to light/moderate drinker</td>
<td>0.91 (0.63, 1.31)</td>
<td>0.34 (0.17, 0.67)</td>
</tr>
<tr>
<td>Light/moderate drinker to heavy drinker</td>
<td>1.02 (0.76, 1.35)</td>
<td>1.00 (0.70, 1.45)</td>
</tr>
<tr>
<td>Heavy drinker to abstainer/light/moderate drinker</td>
<td>1.53 (1.11, 2.10)</td>
<td>0.67 (0.39, 1.14)</td>
</tr>
</tbody>
</table>

*Adjusted for age, systolic blood pressure, serum cholesterol, serum triglycerides, serum uric acid, cigarette smoking (pack-years), coffee intake, and total caloric intake.
†Referent category.
consumption categories examined, slightly more than one third of both middle-aged (38%) and elderly (36%) men reported a change in their alcohol consumption between the time of the initial baseline assessment and reassessment 6 years later. Although the reasons for these alterations in reported alcohol ingestion are unknown, these observations suggest the need for careful assessment and consideration of alcohol intake in clinical and epidemiological studies. As in previous studies, the lack of objective confirmation of actual amount of alcohol consumed, lack of information concerning drinking patterns before baseline assessment, and other possible confounding unmeasured factors, such as psychosocial factors, place appropriate reservations on the observed findings. Inclusion of former drinkers with never-drinkers in the abstainer category requires careful interpretation of findings in this subgroup of men. The relatively small number of elderly men consuming moderate-to-heavy amounts of alcohol and the small number of events in selected analyses place further reservations on the interpretation and extrapolation of the observed findings, with any observed health-related effects of alcohol consumption possibly attributed to random variation in observed rates. Finally, additional concerns need to be placed on the generalizability of the observed findings. These findings were observed in a cohort of Japanese men whose sociodemographic, lifestyle, and dietary characteristics differ from those observed in predominantly Caucasian populations. Moreover, as opposed to the findings typically seen in Caucasian populations in whom the proportion of deaths from coronary heart disease markedly exceeds those from cancer, the proportion of deaths from cancer in the present cohort exceeds those from coronary heart disease by almost twofold. This mortality pattern is most likely a result of the lower incidence rates of coronary heart disease that are characteristic of Japanese populations. Although the incidence of hemorrhagic and thromboembolic stroke is approximately three times higher in Japan than in Japanese-Americans living in Hawaii and the United States in general,38 the proportion of strokes that are hemorrhagic is considerably higher in Japan, where they represent more than one third of all strokes observed.39

Although the specific mechanisms by which alcohol may exert a beneficial effect on overall health have not been clearly elucidated, the results of the present longitudinal study furnish additional insights into this topic and provide a balanced perspective of the detrimental as well as beneficial health effects associated with alcohol consumption.

Consistent with the majority of previously published reports, we observed, albeit nonsignificant overall, trends for a protective effect of light drinking in middle-aged men and moderate drinking in elderly men on total mortality and for harmful effects of excessive alcohol consumption. The finding of a beneficial effect of alcohol consumption on the occurrence of coronary heart disease, with a significant curvilinear dose-response relation observed in middle-aged men, is also consistent with the majority of published investigations examining this issue. An additional finding of importance from this study was the observation in both middle-aged and elderly men of trends for a beneficial effect of very light (1 to 4.9 mL of alcohol per day) drinking on total mortality, cardiovascular mortality, and cancer mortality, with the exception of deaths due to stroke in the elderly. Of the few studies that have stratified for age in examining this association, a beneficial effect of light-to-moderate drinking on the 10-year mortality rate from all causes of death was seen in those 50 to 59 and 60 to 64 years old,5 whereas an additional study found this effect to be strongest among individuals less than 50 years old and comparatively weak among those 60 years old or older.18,40

With the exception of heavy elderly drinkers, increasing alcohol consumption was shown to be positively, although nonsignificantly, associated with fatal and nonfatal events attributed to cerebrovascular disease after controlling for other potentially confounding factors. Previous findings from the Honolulu Heart Program41 as well as those from the Nurses’ Health Study13 have suggested that alcohol consumption is independently associated with the risk of stroke and deaths from stroke. On the other hand, some studies have failed to demonstrate an association between alcohol intake and subsequent risk of stroke,42 whereas a recent study suggested a J-shaped association between alcohol consumption and hemorrhagic and nonhemorrhagic strokes.43 When we examined the association between type of stroke and reported alcohol intake, the risk of hemorrhagic stroke was particularly increased among those consuming alcohol relative to abstainers.

Limited studies have examined the relation between alcohol consumption and risk of dying from cancer. Previous findings from the Honolulu Heart Program have shown that men who drank were more likely to die from cancer,25 whereas findings from the Framingham Heart Study,6 Kaiser-Permanente,9 and the rural Italian cohorts of the Seven Countries Study32 have shown an increased death rate from cancer, with the death rates from stomach cancer being particularly elevated among men who drank heavily and were enrolled in the Framingham Heart Study.6 A number of epidemiological studies have also suggested associations between alcohol consumption and a variety of cancers at different organ sites.44 These findings suggest either a possible direct carcinogenic effect of alcohol or a neoplastic promoting effect of alcohol on other compounds. On the other hand, recent findings from the large longitudinal study of men enrolled in the American Cancer Society study show a slight reduction in cancer mortality for light and moderate drinkers but an increased risk of dying from cancers of the oral cavity and esophagus with increased levels of drinking.14

In summary, the results of the present study provide a balanced overview in which public policy recommendations for alcohol consumption in relation to overall health effects in middle-aged and elderly men might be formulated. Increasing alcohol intake, particularly at high levels of consumption, was shown to be related to an increasing risk of selected fatal and nonfatal events of considerable public health importance. These findings therefore do not provide support for an across-the-board recommendation for a populationwide increase in the levels of alcohol consumed given the significant social and biological problems associated
with high levels of alcohol consumption. Men who are presently consuming light-to-moderate amounts of alcohol and do not appear to be at increased risk for alcohol addiction or abuse should be told to continue their patterns of alcohol consumption given the apparently beneficial effects of light-to-moderate intake of alcohol on coronary heart disease, unless these individuals possess other factors that place them at increased risk for other chronic diseases. These findings reinforce the age-old philosophy of “all things in moderation” as well as the caution to be exercised in association with excessive alcohol ingestion, as succinctly expressed in a Japanese proverb, “First the man takes a drink, then the drink takes a drink, then the drink takes the man.”

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