Alcohol Intake in Middle Age and Risk of Cardiovascular Disease and Mortality: Accounting for Intake Variation over Time

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Moderate alcohol consumption is associated with a decreased risk of cardiovascular disease. However, the impact of variation in alcohol intake over time on estimated risk relations has not been adequately addressed. In this study, 6,544 middle-aged British men without previous cardiovascular disease were followed for cardiovascular events and all-cause mortality over 20 years from 1978/1980 to 1998/2000. Alcohol intake was ascertained at regular points throughout the study. A total of 922 men had a major coronary event within 20 years, 352 men had a stroke, and 1,552 men died of all causes. Baseline alcohol intake displayed U-shaped relations with cardiovascular disease and all-cause mortality, with light drinkers having the lowest risks and nondrinkers and heavy drinkers having similarly high risks. However, the nature of these relations changed after adjustment for intake variation; risks associated with nondrinking were lowered, and risks associated with moderate and heavy drinking increased. Regular heavy drinkers had a 74% higher risk of a major coronary event, a 133% higher risk of stroke, and a 127% higher risk of all-cause mortality than did occasional drinkers (these estimates were 8%, 54%, and 44% before adjustment for intake variation). The findings suggest that considerable caution may be needed before any recommendations regarding acceptable limits of alcohol consumption are made.

alcohol drinking; cerebrovascular accident; coronary disease; mortality

Epidemiologic studies have consistently demonstrated that light to moderate levels of alcohol intake are associated with reduced risks of cardiovascular disease and all-cause mortality (1–4), possibly because of beneficial effects of alcohol on blood lipids (especially high density lipoprotein cholesterol) and clotting factors (5). Heavy alcohol consumption, on the other hand, is associated with increased risks of cardiovascular disease and all-cause mortality, though often the disease risks of heavy drinkers are observed to be only marginally greater than, if not similar to, those of nondrinkers. While the epidemiologic evidence on the relation between alcohol and different diseases is now extensive (3), almost all cohort studies that have estimated these relations have used baseline measures of alcohol intake in analyses. However, because of changing drinking habits in individuals over time and random measurement errors, assessments of alcohol intake taken at baseline may not reflect true usual drinking practices of study participants over the period of risk being studied. Systematic changes and errors in reported alcohol consumption have the potential to change the magnitude and even direction of estimated dose-response relations. While this phenomenon is recognized (6), few epidemiologic studies have been able to directly estimate the impact of these influences on estimated risk associations.

In this paper, data from a prospective study of cardiovascular disease among middle-aged British men (the British Regional Heart Study) are used to examine associations between alcohol intake and the 20-year risk of coronary heart disease, stroke, and all-cause mortality. Using repeated measurements of alcohol intake collected after approximately 5, 13, 17, and 20 years of follow-up, we assessed the impact of individual variation in reported alcohol intake on estimated disease relations.

MATERIALS AND METHODS

The British Regional Heart Study is a prospective study of cardiovascular disease in one general practice in each of
24 British towns (7). In 1978–1980, 7,735 men aged 40–59 years were recruited into the study. Since the baseline assessment (which included a nurse-administered questionnaire, available at www.ucl.ac.uk/primcare-popscl/hrb), men have been followed for all-cause mortality and cardiovascular morbidity, with fewer than 1 percent being lost to follow-up (8). Postal questionnaires were completed by surviving study participants in 1983–1985 (on the fifth anniversary of each participant’s entry into the study), in 1992, and in 1996. Between 1998 and 2000, surviving men were invited to attend a rescreening, at which a further questionnaire was completed. Response rates to the postal questionnaires were high, ranging from 98 percent to 88 percent, while 77 percent of surviving men attended the screening between 1998 and 2000 and completed the questionnaire.

Baseline evidence of cardiovascular disease

Participants completed a World Health Organization (Rose) chest pain questionnaire and were asked about recall of any physician diagnosis of myocardial infarction, stroke, or angina and whether they had ever had a history of severe chest pain lasting half an hour or more that caused them to consult a physician. Individuals with recall of myocardial infarction, angina, or stroke, or with a history of severe chest pain or Rose angina questionnaire evidence of definite or possible angina (or any combination of these), were excluded from analyses.

Baseline assessment of alcohol intake

Alcohol intake, ascertained from questions inquiring about frequency, quantity, and type of alcoholic beverage consumed, was categorized into five groups: 1) nondrinkers; 2) occasional drinkers (1–2 times/month or on special occasions); 3) light drinkers (1–2 drinks/day or “weekend only” drinkers (1–6 drinks/day)); 4) moderate drinkers (3–6 drinks/day or weekend only drinkers (>6 drinks/day)); and 5) heavy drinkers (>6 drinks every day) (9). Twenty-five biochemical and hematologic factors analyzed from a blood sample taken at the time the questionnaire was completed indicated that the reported levels of alcohol consumption were valid on a group basis (10).

Follow-up questionnaires and “average” alcohol intake

At each of the four follow-up questionnaires, surviving participants were asked about their drinking habits, and alcohol intake was recategorized according to the baseline definitions. Using these data, we calculated “average” alcohol intake over the study period (or until the time of first myocardial infarction or stroke, if observed) for each individual. A five-point scale from zero (none) to four (heavy) was used to denote the alcohol intake level at the baseline assessment and at each of the follow-up assessments. Changes in consumption reported between consecutive questionnaires were assumed to occur linearly over the intervening period, unless a major coronary heart disease event or stroke occurred during that period, in which case it was assumed that the individual continued to drink at the same rate as reported at the most recent questionnaire until the date of that event. From these average exposure levels, each individual was reclassified on the original scale (an average exposure of <0.5 was defined as “none,” 0.5–1.49 was defined as “occasional,” 1.5–2.49 was defined as “light,” 2.5–3.49 was defined as “moderate,” and ≥3.5 was defined as “heavy”).

Assessment of incident cardiovascular morbidity and all-cause mortality

Information on incident mortality was collected through the established “tagging” procedures provided by the National Health Service central registers. Fatal coronary events were defined as deaths from ischemic heart disease, including sudden death of presumed cardiac origin (International Classification of Diseases, Ninth Revision, codes 410–414) and fatal strokes as deaths with same-source codes 430–438. Nonfatal heart attacks and strokes were ascertained from general practitioner reports supplemented by systematic reviews of patient records (including hospital and clinic correspondence) every 2 years throughout the study period (11). Nonfatal heart attacks were diagnosed according to established World Health Organization criteria, while nonfatal strokes were defined as all cerebrovascular events that produced a neurologic deficit present for more than 24 hours (12). In this paper, major coronary heart disease events include death from coronary heart disease and nonfatal myocardial infarction.

Statistical analysis

Major coronary heart disease, stroke, and all-cause mortality rates were calculated per 1,000 person years of follow-up and directly standardized to the age distribution of the cohort. Cox proportional hazards regression was used to estimate the age-adjusted hazard ratio of major coronary heart disease, stroke, and all-cause mortality over 20 years by alcohol intake level, from both baseline data (before adjustment for intake variation) and “average” alcohol intake (after adjustment for intake variation). For presentation purposes, hazard ratios were calculated as “floating absolute risks” (13), and inverse variance-weighted quadratic curves were fitted through the values (figure 1). “Occasional” drinkers were used as the referent category in preference to “nondrinkers” because of the problems in separating former drinkers from lifelong teetotalers in the latter group. The “relative informativeness” of baseline versus average alcohol intake was evaluated by examining the contributions made by each measure to the $\chi^2$ likelihood ratio statistic in the Cox regression model (14). Analyses were subsequently repeated after adjustment for cigarette smoking, physical activity, and body mass index, to assess the independent effects of alcohol on cardiovascular and all-cause mortality risk taking into account other important lifestyle characteristics. Analyses were not adjusted for blood pressure or high density lipoprotein cholesterol, as these factors are likely to mediate some of the alcohol-disease relation. The effect of restricting analyses to men who completed all four follow-up questionnaires (or else all
questionnaires prior to their date of first major cardiovascular disease event or death) was assessed in a sensitivity analysis.

RESULTS

Of the 7,735 men recruited into the study, 1,186 (15.3 percent) had baseline evidence of cardiovascular disease (see Materials and Methods) and were excluded from analyses. Of the remaining men, five had incomplete baseline data on alcohol consumption, leaving 6,544 men for analysis.

Alcohol intake over the study period

Information on alcohol intake was obtained for 6,544 men at baseline, for 6,127 men in 1983–1985, for 4,916 men in 1992, for 4,433 men in 1996, and for 3,706 men at the 20-year screening between 1998 and 2000 (table 1). At baseline, 358 men (5.5 percent) were classified as non-drinkers and 696 (10.6 percent) as heavy drinkers. The modal category was “light” drinking, comprising one third of the study cohort, with “occasional” and “moderate” drinkers each contributing approximately one quarter of the men. During the follow-up period, there was a steady downward trend in the amount of alcohol consumption reported by surviving study participants (probably because of a combination of the cohort’s becoming older and drinking less, possible secular changes in alcohol consumption with time, and survival “selection” effects). The result of this was that, by 20 years of follow-up, only 2.8 percent of the surviving men (who responded to the questionnaire) were classified as heavy drinkers while 10.0 percent were classified as nondrinkers.

For each subject, average alcohol intake during his “exposure period” (time until censoring or first cardiovascular event, whichever is lowest) was calculated, and men were reclassified into the original categories. Table 2 shows how the baseline classifications compare with those derived from “average” levels of alcohol consumption. The extent to which men were classified differently based on their baseline and average alcohol intake levels indicates the amount of individual variation in alcohol intake present. Intake variation can be seen to increase with increasing alcohol consumption, as reflected by the observation that 78 percent of those originally defined as nondrinkers were defined the same when based on average levels, compared with 65 percent of those originally defined as light drinkers and only 28 percent of those originally defined as heavy drinkers. Baseline assessment of alcohol exposure resulted in substantial overestimation of the number of men who were truly heavy drinkers during the study period and underestimation of the number of men who, on average, could be classified as nondrinkers.

Alcohol intake and the risk of major coronary heart disease, stroke, and all-cause mortality

The relations between alcohol intake (before and after adjustment for intake variation) and the risk of major coronary heart disease (CHD) (coronary death and nonfatal myocardial infarction), stroke, and all-cause mortality by alcohol intake, among British Regional Heart Study men originally free from cardiovascular disease followed from 1978/1980 to 1998/2000. The black circles and solid line correspond to baseline alcohol intake levels, and the white circles and dashed line correspond to “usual” alcohol intake levels obtained after adjustment for individual variation in alcohol intake. The size of each plotting symbol indicates the amount of statistical information on which each estimate is based; the area is inversely proportional to the variance of the log floating absolute risk. The vertical lines show 95% confidence intervals for the floating absolute risks.
coronary heart disease, stroke, and all-cause mortality over 20 years are shown in figure 1 and table 3. Estimated hazard ratios and confidence intervals are shown relative to occasional drinkers.

**Alcohol and the risk of major coronary heart disease and stroke**

A total of 922 men (14.1 percent) experienced a major coronary heart disease event within 20 years, and 352 men (5.4 percent) experienced a stroke (age-standardized rates of 8.4 and 3.2 per 1,000 person-years, respectively). Before adjustment for intake variation, a shallow U-shaped relation between alcohol intake and major coronary heart disease risk was observed, with “light” drinkers having the lowest risk, 19 percent lower than for occasional drinkers. For stroke, an apparently stronger U-shaped relation was observed (though this could equally be a chance observation), with nondrinkers and heavy drinkers experiencing similarly high stroke risks and light drinkers again experiencing the lowest risk. Adjustment for intake variation increased the estimated benefits for major coronary heart disease risk associated with light drinking to 26 percent, whereas for stroke, the relative differences among nondrinking, occasional drinking, and light drinking groups became small and insignificant. Risks associated with heavy drinking were greatly increased after adjustment for intake variation, however. Relative to occasional drinkers, regular heavy drinkers had a 74 percent higher risk of major coronary heart disease and a 133 percent higher risk of stroke (these estimates were 8 percent and 54 percent, respectively, when derived from baseline exposure). The contribution made by alcohol intake to the likelihood ratio statistics for the prediction of major coronary heart disease and stroke increased markedly after adjustment for intake variation (from 9.4 to 37.0 for major coronary heart disease and from 10.6 to 20.1 for stroke), indicating substantial increases in the “relative informativeness” of alcohol intake for both diseases.

**Alcohol and all-cause mortality**

A total of 1,552 men (23.7 percent) died of all causes within 20 years (age-standardized death rate of 13.7 per 1,000 person-years). Again, a U-shaped relation was observed with baseline alcohol intake. However, taking variation in alcohol intake over time into account caused an increase in the all-cause mortality risks associated with moderate and heavy drinking. Regular heavy drinking was associated with a 127 percent increase in all-cause mortality risk relative to occasional drinkers (44 percent before adjustment for intake variation). Light drinking was associated with the lowest all-cause mortality risk, 18 percent lower than for occasional drinkers. The "relative

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**TABLE 1. Responses to alcohol intake at baseline and after approximately 5, 13, 17, and 20 years of follow-up, British Regional Heart Study, 1978/1980–1998/2000**

<table>
<thead>
<tr>
<th>Reported alcohol intake</th>
<th>Baseline</th>
<th>Follow-up questionnaires of surviving men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>None</td>
<td>358</td>
<td>5.5</td>
</tr>
<tr>
<td>Occasional</td>
<td>1,556</td>
<td>23.8</td>
</tr>
<tr>
<td>Light</td>
<td>2,189</td>
<td>33.5</td>
</tr>
<tr>
<td>Moderate</td>
<td>1,745</td>
<td>26.7</td>
</tr>
<tr>
<td>Heavy</td>
<td>696</td>
<td>10.6</td>
</tr>
<tr>
<td>Total</td>
<td>6,544</td>
<td>100.0</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Baseline assessment of alcohol intake</th>
<th>None</th>
<th>Occasional</th>
<th>Light</th>
<th>Moderate</th>
<th>Heavy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>None</td>
<td>280</td>
<td>78</td>
<td>66</td>
<td>18</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>Occasional</td>
<td>264</td>
<td>17</td>
<td>974</td>
<td>63</td>
<td>307</td>
<td>20</td>
</tr>
<tr>
<td>Light</td>
<td>41</td>
<td>2</td>
<td>562</td>
<td>26</td>
<td>1,421</td>
<td>65</td>
</tr>
<tr>
<td>Moderate</td>
<td>9</td>
<td>1</td>
<td>156</td>
<td>9</td>
<td>842</td>
<td>48</td>
</tr>
<tr>
<td>Heavy</td>
<td>19</td>
<td>3</td>
<td>113</td>
<td>16</td>
<td>366</td>
<td>52</td>
</tr>
<tr>
<td>Total</td>
<td>594</td>
<td>9</td>
<td>1,777</td>
<td>27</td>
<td>2,694</td>
<td>41</td>
</tr>
</tbody>
</table>
informativeness” increased nearly threefold by taking intake variation into account (the likelihood ratio contribution increased from 38.2 to 101.3).

**Effect of adjustment for other lifestyle risk factors**

The primary analyses were repeated after adjustment for body mass index, physical activity, and cigarette smoking, factors known to be related to both alcohol consumption and the risk of cardiovascular disease and all-cause mortality (15). The shape of the disease relations with usual alcohol intake was essentially unchanged by adjustment for these factors, though the excess risks from moderate and heavy drinking were reduced. After adjustment for body mass index, physical activity, and cigarette smoking, but before adjustment for variation in alcohol intake over time, heavy drinkers appeared to have a 17 percent lower risk of major coronary heart disease, a 27 percent higher risk of stroke, and a 15 percent higher risk of all-cause mortality compared with occasional drinkers. After adjustment for variation in alcohol intake, however, risks among heavy drinkers were, respectively, 32 percent, 86 percent, and 70 percent higher than for occasional drinkers.

**Sensitivity analysis**

When analyses were restricted to the 4,536 men (69.3 percent) who completed all four follow-up questionnaires (or all questionnaires up to their first major cardiovascular disease event or death), the estimated disease risks for heavy drinkers relative to occasional drinkers increased still further, though confidence intervals were, of course, wider (results available from authors on request).

**DISCUSSION**

In middle-aged British men with no previous evidence of cardiovascular disease, after adjustment for individual variation in intake, regular light alcohol consumption was associated with a statistically significant 26 percent reduced risk of coronary heart disease and 18 percent reduced risk of all-cause mortality, as well as a statistically insignificant 7 percent reduced risk of stroke (compared with occasional drinkers). Moderate drinking and heavy drinking, on the other hand, were associated with substantially increased risks of stroke, all-cause mortality, and (to a lesser degree) major coronary heart disease. Stroke and all-cause mortality risks were more than twice as high among heavy drinkers than among occasional drinkers, while major coronary heart disease risk was 74 percent higher in this group (all p’s < 0.001). However, before variation in alcohol intake over time was taken into account, only moderate differences in stroke and all-cause mortality risks between heavy drinkers and occasional drinkers were observed (with no significant differences in major coronary heart disease risk).

**Validity of methods**

In this paper, it was possible to relate 20-year cardiovascular and all-cause mortality risks to average alcohol intake.
during the study because, in addition to the baseline assessment, alcohol intake was reassessed in a high proportion of surviving men after approximately 5, 13, 17, and 20 years of follow-up. These repeated assessments allowed estimation of “usual” alcohol intake over the study period for each individual. Crucially, because only information on alcohol consumption that was recorded while the subject was still at risk of a first major cardiovascular event was used in this process, our results are unlikely to be affected by reverse causality bias (the effect on the alcohol-disease relation that could otherwise be caused by nonfatal cardiovascular events leading to subsequent change in drinking pattern). Alternatively, we could have fitted alcohol consumption as a “time-dependent” covariate, that is, a variable that could change value at the time each questionnaire was completed. However, because of the fairly long intervals between successive questionnaires as well as the desire to use information gained from the 20-year questionnaire in our analyses (information which would effectively be redundant in any time-dependent approach), it was decided to use the information gained from each individual to create a single measure that best represented his usual alcohol intake exposure during the study period. Our method of analysis should therefore provide reliable estimates of the true relations between long-term “usual” alcohol consumption patterns and the development of cardiovascular disease and the risk of death. However, it is possible that some men may have reduced their alcohol intake from “moderate” or “heavy” drinking to “light” drinking because of ill health short of major cardiovascular disease. If these men were subsequently classified as “light” drinkers on the basis of usual average intake, that could change value at the time each questionnaire was completed.

Comparison with other studies

Consistent with the estimated risk-relations presented in this paper before adjustment for individual alcohol intake variation, systematic reviews of the effects of alcohol on mortality risk have consistently shown either U- or J-shaped relations between alcohol consumption and the risk of cardiovascular disease and all-cause mortality (1–4). With light to moderate drinkers experiencing 25–35 percent lower risks than nondrinkers and heavy drinkers experiencing risks similar to those of nondrinkers (though the evidence for a protective effect of moderate alcohol on stroke is less clear) (17). In the Whitehall II study of British civil servants, for instance, moderate drinkers had approximately half the 11-year risk of death from coronary heart disease and all causes compared with either nondrinkers or heavy drinkers (18), while in the British Doctors’ Study (6), coronary heart disease death rates were 43 percent lower for men who drank 15–21 units of alcohol a week (compared with nondrinkers), death rates from stroke were 17 percent lower, and deaths from all causes were 28 percent lower (men who drank at least 43 units of alcohol a week had similar death rates to those of nondrinkers). Several very large US cohort studies, including the Physicians’ Health Study (19), the Nurses’ Health Study (20), Cancer Prevention Study II (21), and the Multiple Risk Factor Intervention Trial (22), have found similar associations between alcohol intake and the risk of cardiovascular disease and all-cause mortality, and they have confirmed that these relations exist in women as well as men (20, 21). Previous reports from the British Regional Heart Study have drawn attention to the strong downward trend with increasing age, from heavy or moderate drinking to light, occasional, or nondrinking status, affected to a considerable extent by the accumulation of ill health over time (23, 24). Reduction in alcohol intake or giving up drinking is associated with higher rates of new diagnoses and increased cardiovascular and noncardiovascular mortality than remaining stable (23). Attention has also been drawn to the disadvantages of using the nondrinkers (lifelong teetotalers and former drinkers) as a referent group, as this may lead to further exaggeration of the protective effect of regular light/moderate drinking (24).
However, most previous studies have used only baseline measures of alcohol consumption in analyses and have not attempted to quantify the role that individual variation in alcohol intake could play, although in the British Doctors’ Study, a reasonable degree of consistency between alcohol intake at the beginning and end of the study suggested that their results may have been fairly robust to these effects (6). Of the studies that have attempted to take changes in individual drinking patterns into account, most have used just two assessments of alcohol intake, and findings have been inconsistent (25, 26). In the MONICA-Augsburg cohort, for instance, it was found that the estimated benefits of light alcohol consumption increased after taking the second measure of alcohol consumption into account (26), while in the First National Health and Nutrition Examination Survey, no elevated mortality was observed when consistent never drinkers were compared with light drinkers (25). In the Health Professionals Follow-up Study, assessment of alcohol intake every 4 years allowed examination of the effects of changes in alcohol consumption on the 12-year risk of myocardial infarction. In this large American study, the beneficial effects of alcohol consumption on the risk of myocardial infarction estimated using baseline measurements were found to be similar to estimates derived from analyses that fitted alcohol consumption as a “time-dependent” covariate (27). However, three other large American studies have demonstrated that baseline measures of drinking groups may be particularly unreliable for younger samples, longer follow-up, and heavier drinkers (28).

Implications for epidemiologic studies

Prospective observational studies help to evaluate the strength and shape of relations between risk factors and the development of disease. However, by relying solely on risk factor measurements taken at a single point in time, true long-term differences in disease risk between risk groups can become imprecisely assessed because of exposure variation over time. It is well recognized that within-person variation in continuous risk factors, such as blood cholesterol and blood pressure, tends to lead to underestimation of true risk associations (29, 30). Similarly, we have found that cardiovascular disease risks associated with heavy cigarette smoking and physical inactivity can also be underestimated when baseline measures are used in analyses (31). In this paper, adjustment for intake variation led to an increase in the risks associated with moderate, and particularly with heavy, drinking. Epidemiologic studies, and in particular those with long follow-up periods, should therefore endeavor to determine whether any systematic changes in risk exposure during the study have occurred. A range of approaches, including the method described in this paper, may be used to examine the effect that these changes may have on estimated disease associations.

Conclusions

The results in this paper suggest that previous prospective studies may have overestimated the benefits for cardiovascular and, particularly, all-cause mortality risk from moderate alcohol consumption. Furthermore, it is suggested that the risks associated with heavy drinking may have been systematically underestimated in previous prospective studies (because of the small proportion of men who tend to remain heavy drinkers over a prolonged period of time). The potential for excess disease risks caused by heavy drinking to be greatly underestimated (or even completely missed) when using baseline assessments of alcohol intake in analyses is particularly worrying. Unless information from follow-up assessments of alcohol consumption is used in analyses, it is likely that prospective observational studies, and in particular those with long follow-up periods, will continue to systematically underestimate these risks. While some of the effect sizes presented in this paper may be exaggerated by the role of chance, the results suggest that considerable caution may be needed before any recommendations regarding acceptable limits of alcohol consumption are made.

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REFERENCES


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