Alcohol Intake and Insulin Levels
The Normative Aging Study

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Much remains to be clarified in the apparently protective effect of moderate alcohol use against coronary heart disease risk. Insulin levels are positively associated with coronary heart disease risk, so recent reports of decreased insulin sensitivity among nondrinkers and lower fasting insulin levels with increasing alcohol intake suggest the possibility that insulin may play a role. Between 1987 and 1991, the authors examined fasting insulin concentrations and the empiric fasting insulin resistance index in relation to reported alcohol intake (mean, 15.3 g/day; standard deviation, 19.6; range, 0–120.6) and potential confounders. The latter included age, obesity, fat distribution, smoking, energy, saturated fat intake, antihypertensive medication, and physical activity. Participants in this cross-sectional analysis were 938 nondiabetic men from the Boston, Massachusetts, area who were part of the Normative Aging Study. Unadjusted fasting insulin levels were significantly different (p = 0.008) between categories of alcohol intake, as were fasting insulin resistance index values (p = 0.01). After adjustment for potential confounders, analysis revealed that subjects consuming moderate amounts of alcohol had the lowest fasting insulin and fasting insulin resistance index values. Compared with values from moderate drinkers, fasting insulin resistance index values were higher in those subjects reporting no alcohol intake (p = 0.011), low intake (p = 0.004), and high intake (p = 0.04). A similar pattern was observed for fasting insulin values. Among this sample of nondiabetic men, moderate drinkers had the lowest levels of fasting insulin resistance index and fasting insulin, consistent with lower levels of insulin resistance and thus lower risk for coronary heart disease. These findings suggest the possibility that the coronary heart disease-protective effects of moderate alcohol use are at least partially mediated by insulin. Am J Epidemiol 1997;145:909–16.

alcohol drinking; coronary disease; insulin; risk factors

Much remains to be clarified with regard to the protective effect of moderate habitual alcohol use against coronary heart disease risk (1). One plausible partial explanation (2) is that the lower coronary heart disease rates observed in subjects with low to moderate levels of alcohol intake are mediated by increased levels of high density lipoprotein cholesterol (3–5).

Substantial elevations in the risk of incident coronary heart disease during 11.5 years of follow-up were reported among middle-aged British men in the top decile of nonfasting serum insulin (6), so recent reporting of lower insulin sensitivity among nondrinking men and women (7) and of lower fasting insulin levels with increasing alcohol intake in women (8) raises the possibility that insulin may also play a role.

Hyperinsulinemia is known to be associated with increased levels of coronary heart disease risk factors including unfavorable blood lipid profiles, hypertension, and obesity (9). The high risk constellation of coronary heart disease risk factors including hyperglycemia, hypertension, and dyslipidemia combined with hyperinsulinemia (10) is now well known. Insulin resistance and associated hyperinsulinemia may also have a role in the development of coronary heart disease risk factors including “essential” hypertension (11, 12) and non-insulin-dependent diabetes mellitus (13, 14). Thus, insulin resistance may be a factor implicated in coronary heart disease as well as a range of other disorders (15).

The purpose of this paper was to explore the relation between measures of insulin resistance and alcohol intake among subjects of the Normative Aging Study. We hypothesized that lower levels of insulin resistance were associated with moderate alcohol intake.
the evidence that moderate alcohol intake may be associated with lower levels of insulin resistance and that insulin resistance is associated with increased levels of coronary heart disease risk factors, this hypothesis is of interest since it implies that lower levels of insulin resistance may at least partially explain the apparently protective effect of moderate alcohol intake.

MATERIALS AND METHODS

Subjects and measurements

The Normative Aging Study was established by the Veterans Administration in 1961. Details of the study protocol have been described previously (16). Briefly, the study cohort comprised 2,280 community-dwelling men from the Boston area who were aged 21–80 years at entry. Volunteers were screened according to specific clinical, laboratory, radiologic, electrocardiographic, and medical history criteria (16), so that all subjects were free of known chronic medical conditions at entry.

Each participant reports for a periodic examination at intervals of 3–5 years, comprising a uniform medical history and physical examination in addition to blood and urine tests. Subjects fast overnight before their examination. A glucose load of 100 g was administered orally after blood had been taken while fasting. Two hours after the glucose load, postchallenge blood was taken. Participants were classified according to World Health Organization criteria (17) as having non-insulin-dependent diabetes mellitus (fasting serum glucose ≥ 7.8 mmol/liter or postcarbohydrate challenge glucose > 11.1 mmol/liter) or glucose intolerance (fasting glucose < 7.8 mmol/liter together with post-carbohydrate challenge glucose between 7.8 and 11.1 mmol/liter) or as being normal (all other combinations of fasting and post-carbohydrate challenge glucose levels). While the World Health Organization criteria are based on an oral glucose load of 75 g (17), an oral load of 100 g (specified in the original study protocol and adhered to for the entire study duration) has been found to produce indistinguishable 2-hour post-carbohydrate challenge plasma glucose values among healthy subjects (18). Although the actual extent of misclassification resulting from the larger load is not known, its direction is likely to have been that some glucose-intolerant subjects may have been falsely excluded on grounds of non-insulin-dependent diabetes mellitus.

Anthropometry was performed with the subject standing erect with feet together, clothed in undershorts and socks only. Weight in pounds was measured on a beam balance and converted into kilograms. Stature was measured against a wall chart. Body mass index was calculated as weight (kg)/height (m²). The waist circumference was measured in a plane perpendicular to the long body axis. The circumference of the hips was measured at the level of the greatest gluteal protuberance. The ratio of the circumference of the waist to the circumference of the hips was calculated as a measure of the distribution of adiposity.

Information on tobacco use was collected by interview. Smoking status was defined as one of three categories: never smoker, current smoker (at least one cigarette a day), or former smoker (not smoking for at least 30 days prior to the visit). Information on dietary habit over the past 12 months was collected using a semiquantitative food frequency questionnaire (19, 20). Daily intake of alcohol was estimated according to the average number of grams of ethanol in the usual serving size for each type of alcoholic beverage. A questionnaire on usual physical activity based on the scale of Paffenbarger et al. (21) was used to estimate weekly energy expenditure (kcal/week) due to physical activity, estimated from the number of flights of stairs climbed and the frequency of various physical activities each day.

During the period from February 1987 to July 1991, serum insulin levels from fasting and postcarbohydrate challenge blood samples were determined using a solid-phase iodine-125 radioimmunoassay (Coat-A-Count Insulin 1987; Diagnostic Products Corp., Los Angeles, California). The interassay and intraassay coefficients of variation for insulin were 5–7 percent and 3–5 percent, respectively. Only participants who were examined during the period when insulin was being measured were eligible for inclusion in this study.

The empiric fasting insulin resistance index was calculated for each subject as the product of fasting insulin and fasting plasma glucose and was normalized to a sample mean value of 1.0 by dividing by the product of the mean values for fasting insulin and fasting glucose (22). Note that this denominator of 419.35 differs from the originally published value of 25 (22), because our insulin data were in Système International d’unités (SI units).

Exclusions

Of the original cohort, 461 men were deceased, 227 had dropped out of the ongoing study, 313 were participating by completing questionnaires only, and 10 had been lost to follow-up, leaving 1,269 potential subjects, of whom 46 were not examined during the relevant period.

A total of 1,223 subjects had at least one fasting blood insulin value recorded and so were eligible for
study. Of these potential participants, 136 men who had either a physician diagnosis of diabetes mellitus or who were taking antidiabetic medication at the time of insulin measurement were excluded. An additional 63 men with laboratory results consistent with non-insulin-dependent diabetes mellitus by World Health Organization (17) criteria were excluded as were 149 subjects with one or more missing values needed for the analysis, leaving a total of 938 subjects with complete data available for this study. Comparison of the group excluded because of missing values with the final study group by unpaired t tests showed that those excluded because of missing values did not differ significantly in terms of age, smoking, dietary values, or anthropometric values but had higher fasting insulin (mean log insulin of 4.43 compared with 4.18, \( p = 0.0001 \)) and lower physical activity (1,939.6 kcal/week compared with 2,510.2, \( p = 0.01 \)).

**Analysis**

We hypothesized that there would be a lower fasting insulin resistance index and fasting insulin levels among moderate drinkers compared with men drinking larger or smaller amounts of alcohol. Natural logarithms of fasting insulin values were used in the analysis, because this transformation greatly decreased the skew noted in the distribution of the untransformed variable.

Spearman’s rank correlation coefficients were estimated between the continuous variables of interest including insulin, fasting insulin resistance index, daily alcohol intake, and potential continuous confounders including body weight, body mass index, waist/hip circumference ratio, age, physical activity level, daily saturated fat intake, and daily energy intake. Marginal association of smoking status with the alcohol intake category was tested by the \( \chi^2 \) statistic. Binary indicator variables for exsmoking and currently smoking status were included in models (with lifelong nonsmokers as the referent groups) to control for confounding by cigarette smoking, because smoking may be associated with insulin resistance (23).

Treatment of preexisting hypertension may include advice to change risk factors including alcohol intake. This potential confounding was explored using unpaired \( t \) tests and stratified analysis. Daily dietary saturated fat intake was adjusted for total energy intake by means of linear regression of saturated fat on total energy intake (24), because the unadjusted measure was highly correlated with total energy intake.

Although alcohol was measured as a continuous variable, a substantial number (\( n = 191 \)) of the subjects reported no alcohol intake, and no transformation could be found that approximated the normal distribution. Usual alcohol intake was categorized into four categories: none, low (0.1 or greater but less than 10 g/day), moderate (10 or greater but less than 30 g/day), and high (30 or more g/day). Differences in unadjusted insulin levels among alcohol intake categories were tested with a one-way analysis of variance. Least-square mean insulin levels for each alcohol intake category were estimated using the SAS (25) GLM procedure, with adjustment for potential confounders, and \( t \) tests were used to test hypotheses about differences among these adjusted means.

**RESULTS**

Means and standard deviations for continuous variables and proportions for categorical variables are shown by alcohol intake category in table 1. One-way analysis of variance by alcohol category for each of the continuous variables shown in table 1 suggested a significant alcohol category class effect for age (\( p = 0.0001 \)), log fasting insulin (\( p = 0.0078 \)), fasting insulin resistance index (\( p = 0.0096 \)), waist/hip circumference ratio (\( p = 0.02 \)), physical activity (\( p = 0.037 \)), and daily energy intake (\( p = 0.0001 \)), but not for weight, body mass index, or energy-adjusted daily saturated fat intake. The dose-response relation between alcohol intake and both the fasting insulin resistance index and fasting insulin appeared to be nonlinear, because subjects drinking moderate amounts of alcohol had the lowest values, while those drinking smaller or larger amounts tended to have higher values.

The mean daily alcohol intake was 15.3 g/day (standard deviation, 19.6; range, 0–120.6), and the distribution was substantially skewed with a median of 7.8 g. Only 90 (9.6 percent) of the subjects were currently smoking tobacco, but more than half (59.7 percent) were exsmokers. The alcohol category was significantly associated with smoking status by \( \chi^2 \) test (\( p < 0.0001 \)). Alcohol intake was significantly higher among current smokers by unpaired \( t \) test (20.1 g/day compared with 14.6 g/day, \( p = 0.03 \)).

More than a quarter of the subjects (\( n = 248, 26.4 \) percent) were taking antihypertensive medication. Compared with those not taking antihypertensive medication, these men had higher values for log fasting insulin (4.27 compared with 4.16 log pmol/liter, \( p = 0.005 \)) and the fasting insulin resistance index (1.103 compared with 0.981, \( p = 0.0071 \)) by unpaired \( t \) test, but their alcohol intake was not significantly different (14.2 compared with 15.7 g/day, \( p = 0.25 \)).

Spearman’s rank correlations between the major continuous study variables are shown in table 2. Alcohol intake was significantly but weakly correlated with both the fasting insulin resistance index and fast-

<table>
<thead>
<tr>
<th>Alcohol Intake Category</th>
<th>Age (years)*</th>
<th>Fasting Insulin (pmol/liter)</th>
<th>Fasting Glucose (mmol/liter)</th>
<th>FIRI*,†</th>
<th>Weight (kg)</th>
<th>BMI† (kg/m²)</th>
<th>WHR*,†</th>
<th>Physical Activity (kcal/week)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (0 g/day)‡</td>
<td>64.9 8.7</td>
<td>77.9 41.6</td>
<td>5.58 0.59</td>
<td>1.05 0.60</td>
<td>80.9 12.0</td>
<td>27.3 3.6</td>
<td>0.992 0.054</td>
<td>2,191 2,040.9</td>
</tr>
<tr>
<td>Low (0.1–9.9 g/day)§</td>
<td>62.8 7.8</td>
<td>80.9 49.6</td>
<td>5.52 0.57</td>
<td>1.08 0.69</td>
<td>82.2 12.2</td>
<td>27.8 3.9</td>
<td>0.990 0.050</td>
<td>2,400 2,017</td>
</tr>
<tr>
<td>Moderate (10.0–29.9 g/day)¶</td>
<td>62.9 7.6</td>
<td>68.1 34.8</td>
<td>5.52 0.54</td>
<td>0.91 0.50</td>
<td>81.6 11.6</td>
<td>27.3 3.5</td>
<td>0.993 0.051</td>
<td>2,702 2,423</td>
</tr>
<tr>
<td>High (£30 g/day)#</td>
<td>61.2 7.3</td>
<td>74.3 43.0</td>
<td>5.59 0.61</td>
<td>1.01 0.63</td>
<td>82.2 10.4</td>
<td>27.4 2.9</td>
<td>1.003 0.052</td>
<td>2,557 2,506</td>
</tr>
<tr>
<td>All**</td>
<td>63.0 7.9</td>
<td>75.7 43.4</td>
<td>5.54 0.58</td>
<td>1.01 0.62</td>
<td>81.8 11.7</td>
<td>27.5 3.6</td>
<td>0.994 0.051</td>
<td>2,487.5 2,237</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Energy Intake (kcal/day)*</th>
<th>Alcohol Intake (g/day)</th>
<th>Saturated fat (g/day)</th>
<th>Current smokers (%)</th>
<th>Never smokers (%)</th>
<th>Exsmokers (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean  SD</td>
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<td>Mean  SD</td>
</tr>
<tr>
<td>None (0 g/day)</td>
<td>1,859 618.9 0</td>
<td>21.8 9.2</td>
<td>33.0 57.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (0.1–9.9 g/day)</td>
<td>1,911 565.0 4.4</td>
<td>21.9 9.0</td>
<td>40.0 54.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate (10.0–29.9 g/day)</td>
<td>1,995 601.0 16.4</td>
<td>22.9 9.8</td>
<td>24.3 65.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High (£30 g/day)</td>
<td>2,195 574.8 49.5</td>
<td>23.3 10.1</td>
<td>20.6 64.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>1,977 598.2 15.3</td>
<td>22.4 9.5</td>
<td>30.7 59.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Means significantly different at p ≤ 0.01 among alcohol classes.
† FIRI, fasting insulin resistance index; BMI, body mass index; WHR, waist/hip circumference ratio; SD, standard deviation.
‡ n = 191.
§ n = 281.
¶ n = 520.
# n = 247.
** n = 938.
Adjusted levels among those reporting no alcohol intake were nonsignificantly higher levels among subjects in the heavy intake category \((p = 0.30)\). A similar analysis stratified by antihypertensive medication status showed essentially the same pattern seen in table 3 in both strata although, among the relatively small stratum of men on antihypertensive medication, none of the comparisons among alcohol intake categories were statistically significant (results not shown).

**DISCUSSION**

In this cross-sectional analysis, a significant association between reported alcohol intake and crude markers of insulin resistance was observed. The relation did not appear to be linear because the lowest levels of the fasting insulin resistance index and fasting insulin were found among moderate drinkers. These differences persisted after adjustment for the major factors known to be associated with insulin levels, including the use of antihypertensive medication, age, smoking status, dietary energy, saturated fat intake, body mass index, the waist/hip circumference ratio, and physical activity.

There is a substantial body of evidence from cohort studies that the relation between alcohol intake and coronary heart disease risk is nonlinear, with the lowest rates of coronary heart disease observed among those drinking one or two drinks a day \((26, 27)\), which corresponds approximately to the moderate \((10-29.9 \text{ g/day})\) category reported here. Given recent reporting of substantially elevated risk of incident coronary heart disease among British men with higher serum insulin levels \((6)\), our finding of a lower fasting insulin resistance index and fasting insulin levels in moderate drinkers suggests that one of the mechanisms by which moderate alcohol intake protects against coronary heart disease could be mediated by insulin.
Limitations

The measure of exposure used in this study was daily alcohol intake derived from a semiquantitative food frequency questionnaire that asked about average intake over the previous 12 months. The limitations of this method are well known (28), and random measurement error is likely to have contributed a bias toward a finding of no effect, so that the estimates of effect we have found are probably conservative.

Systematic error may also be present because it is probable that some heavy drinkers underreported their alcohol intake. The measurement of alcohol intake over the past 12 months may be a poor measure of lifelong exposure to alcohol. It is also likely that the group of nondrinkers or light drinkers includes some former heavy drinkers. This issue, which our data were not able to address, has been identified as a potential source of bias in many studies of alcohol and cardiovascular disease (29).

The sample studied here was drawn from a cohort that comprised male volunteers, most of whom were middle-aged or older. Subjects excluded because of missing values had significantly higher fasting insulin levels. The extent to which the results were biased by their exclusion is not clear. Although the analysis was adjusted for smoking status, residual confounding from tobacco smoking may have been present because smoking was significantly associated with alcohol intake in our data and has been shown to be associated with insulin resistance in the literature (23).

Alcohol intake may be affected by ill health or knowledge of a medical condition associated with hyperinsulinemia. One obvious candidate is preexisting hypertension, because medical advice to patients on antihypertensive medication is likely to include alcohol restriction. As in other cohorts (9), Normative Aging Study subjects taking antihypertensive medication had significantly higher fasting insulin levels, and adjustment for antihypertensive status was included in the analysis. Hence, bias from this source is not likely to explain our findings. A similar pattern was observed in a stratified analysis, although the findings were not statistically significant in the relatively small stratum of subjects using antihypertensive medication.

Insulin and the fasting insulin resistance index as measures of insulin resistance

The fasting insulin resistance index is a simplified transformation of the formula for homeostasis model assessment of insulin resistance (22). Homeostasis model assessment gives estimates of insulin resistance that are very highly correlated with results from the hyperinsulinemic euglycemic clamp (r = 0.88 in a group of 11 diabetic and 12 normal subjects) (30). Fasting insulin values have also been shown to be strongly correlated with specialized laboratory measures of insulin resistance, particularly in nondiabetic subjects such as those studied here (31, 32).

Although specialized measures of insulin resistance were not available from the Normative Aging Study cohort, it seems reasonable to suggest that our findings on the fasting insulin resistance index and fasting insulin reflect differences in underlying insulin resistance.

Alcohol and insulin resistance

Previous reports of the acute effects of relatively large doses of ethanol on measures of insulin sensitivity have shown impaired insulin-mediated glucose uptake (33, 34). However, it seems that the chronic effects of moderate ethanol intake may be quite the opposite. A significant negative unadjusted correlation between alcohol intake and log insulin (r = -0.07) was reported from a large group of young adults (35) and in elderly males in the Honolulu Heart Study (r = -0.05) (36), but these findings were not explored in detail. In a study of women twins (8) with relatively low levels of alcohol use (median intake = 4.1 g/day), a negative relation between alcohol intake and both fasting and post-glucose load insulin levels was found. The sample included very few heavy users of alcohol.

In a sample based on a newspaper advertisement in which there was comparison of nondrinkers with users of moderate amounts of alcohol, lower levels of fasting and post-carbohydrate challenge insulin (significance not reported) and significantly greater steady-state plasma glucose values were found (7). The analysis was unadjusted, and the sample included neither light nor heavy alcohol users, so the dose-response relation between alcohol intake and insulin levels could not be explored.

Although the rank correlations between alcohol intake and markers of insulin resistance (the fasting insulin resistance index and fasting insulin) shown in table 2 are of small magnitude, these linear correlations will underestimate a nonlinear dose-response relation. The adjusted mean values shown in table 3 suggest that the dose-response relation is not linear. The biologic mechanism by which moderate levels of alcohol intake lead to lower levels of insulin resistance is not known.

Insulin resistance and coronary heart disease

A body of evidence implicating insulin resistance in a related group of coronary heart disease risk factors including essential hypertension and dyslipidemia has
recently been reviewed (15). If insulin resistance is lower in moderate drinkers, then lower levels of coronary heart disease risk may be mediated by associated changes in coronary heart disease risk factors associated with insulin resistance. Higher levels of high density lipoprotein cholesterol observed among moderate drinkers (3–5) may be an example of this effect.

Conclusions

The findings reported here from nondiabetic men suggest that moderate alcohol use may be associated with lower levels of insulin resistance than is observed among those reporting greater or lesser amounts of alcohol intake. The relation between alcohol intake and measures of insulin resistance (fasting insulin resistance index and fasting insulin) persisted after adjustment for potential confounders including age, obesity, body fat distribution, treatment for hypertension, cigarette smoking, physical activity, dietary saturated fat, and energy intake. Both the fasting insulin resistance index and fasting insulin values have been shown to correlate reasonably well with specialized laboratory-based measures of insulin resistance.

Lower levels of insulin resistance imply lower levels of associated coronary heart disease risk factors, so our findings are consistent with the possibility that lower levels of insulin resistance may be one of the mechanisms mediating the apparently protective effect of moderate alcohol use on coronary heart disease risk. Given that there are many risks associated with both acute and chronic alcohol use, this finding must be interpreted in a larger public health context, where coronary heart disease is only one line entry in the complex risk-benefit balance sheet for alcohol consumption.

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