Alcohol Consumption and Insulin Concentrations
Role of Insulin in Associations of Alcohol Intake With High-Density Lipoprotein Cholesterol and Triglycerides

Elizabeth J. Mayer, PhD; Beth Newman, PhD; Charles P. Quesenberry Jr, PhD; Gary D. Friedman, MD; Joseph V. Selby, MD, MPH

Background. The relation between alcohol intake and insulin levels may explain, in part, the reported associations of alcohol with cardiovascular disease risk factors, including high-density lipoprotein (HDL) cholesterol, triglycerides, blood pressure, and glucose levels, each of which has been recognized as a component of the insulin resistance syndrome.

Methods and Results. Subjects included nondiabetic participants of the Kaiser Permanente Women Twins Study (1989 through 1990). Usual alcohol intake was assessed as part of a food frequency questionnaire. For women from 98 monozygotic twin pairs in which both twins drank (n=338), an increment of 12 g of alcohol per day (about one drink) was associated with an 8% lower 2-hour post–glucose-load insulin (P<.01) in a multiple regression analysis for twin data, adjusted for age, body mass index, waist-to-hip ratio, total caloric intake, and family history of diabetes. With genetic influences removed by matched analysis of the subset of 98 monozygotic twin pairs, an intrapair difference of 12 g of alcohol per day was associated with a 12.4% intrapair decrement in postload insulin (P<.01). Inverse associations were also seen for fasting insulin. Alcohol consumption was inversely associated with postload glucose but not with fasting glucose in unmatched (P=.05) and matched (P=.005) analyses. A significant positive association of alcohol intake with high-density lipoprotein cholesterol and an inverse relation of alcohol intake with triglycerides were each independent of insulin levels (P<.02 in the matched models). Neither systolic nor diastolic blood pressures were related to alcohol consumption in this sample, perhaps because of the rather low level of alcohol intake in the study population (median, 4 g/d).

Conclusions. Within the range of light to moderate drinking habits, alcohol consumption was inversely related to fasting and postload insulin levels. This relation did not explain associations of alcohol intake with lipid levels and may instead reflect an additional mechanism by which moderate alcohol consumption impacts cardiovascular disease risk. (Circulation. 1993;88[part 1]:2190-2197.)

KEY WORDS • lipids • blood pressure • glucose

Persons who consume low or moderate amounts of alcohol appear to experience lower incidence of coronary heart disease (CHD) compared with those who abstain, and CHD mortality is reduced among moderate drinkers compared with either abstainers or persons who drink heavily.1,4 The positive effect of alcohol consumption on high-density lipoprotein cholesterol (HDL-C)5 has been proposed as a possible protective mechanism.6 Acutely, alcohol can elevate triglycerides,7 but reports of the long-term effect of moderate alcohol ingestion are conflicting.8-11 A causal relation between heavy alcohol consumption and hypertension is well supported,12,13 although the effect of light to moderate drinking on blood pressure is less clear.8,12 Heavy drinking also may increase risk for non–insulin-dependent diabetes mellitus (NIDDM),14 but again, data related to the effect of light to moderate drinking on glucose levels are equivocal.14-16

Each of the above outcomes has been related to levels of circulating insulin. Insulin resistance and increased insulin concentrations have been associated with lower levels of HDL-C, higher triglycerides, obesity, and elevated risk for hypertension, NIDDM, and CHD.17,18 Therefore, evaluation of usual alcohol intake in relation to insulin levels may help to explain how alcohol may impact these outcomes. In 1974, Ostrander et al19 noted that insulin may mediate the hypertriglyceridemic effect of alcohol consumption but found no association between alcohol intake and insulin levels. More recently, Manolio et al19 reported a negative correlation between alcohol intake and fasting insulin among a sample of young adults.

We evaluated the associations of usual alcohol intake with fasting and post–glucose-load insulin concentrations among nondiabetic women twins. The possible...
role of insulin in associations of alcohol intake with HDL-C, triglycerides, and blood pressure was then considered. Since both insulin levels and alcohol intake may be under genetic influence to some extent, we also examined associations within a subset of monozygotic twin pairs to evaluate our findings after removal of genetic influences by matched pair analyses.

Methods

Subjects

The first examination of the Kaiser Permanente Women Twins Study was conducted in 1978 through 1979 and included 434 twin pairs. Of the original cohort, 90% were white. Zygosity for each pair was determined by analysis of 20 polymorphic loci such that the probability of misclassification as monozygotic was < .001.\(^2\)

The 352 pairs (81.1%) who were reexamined approximately 11 years later constitute the subjects of this report. Each woman provided informed consent for all components of the study. The study protocol was approved by the Kaiser Permanente Medical Care Program, Northern California Region, Institutional Review Board. Analyses used data collected at the second examination and were restricted to women who were not diabetic, in part because subsequent modifications to alcohol intake could bias associations under study in the present report. Forty-nine women were excluded because they met the World Health Organization (WHO) criteria for diabetes based on a 75-g oral glucose tolerance test\(^2\) or because of reported current use of insulin or oral hypoglycemics. An additional 23 women were excluded because diabetes could not be ruled out (WHO-defined diabetes status uncertain or status unknown because of missing glucose values, n=10; or self-reported physician diagnosis of diabetes, n=13). In addition, 24 pregnant or lactating women were excluded. Twins of excluded women were also eliminated (n=64) as required for analyses of twin data. After exclusion of one woman (and her twin) who reported unusually high alcohol intake (approximately 16 drinks per day), the final sample included 542 women, with 163 monozygotic pairs and 108 dizygotic pairs. Sample sizes varied slightly for some analyses because of occasional missing values.

Measurements

Alcohol intake during the month before the clinic visit was included as part of a self-administered food frequency questionnaire,\(^2\) modified by the use of a defined frequency response set rather than open-ended responses and the addition of a small number of commonly consumed foods. Participants indicated their average use of wine, beer, and liquor separately by checking one of nine responses that ranged from never to six or more drinks per day. Serving size was queried relative to a "medium" portion, with "small" defined as 0.5 times the medium portion and "large" defined as 1.5 times the medium portion.\(^2\) To account for differences in alcohol content for different types of alcoholic beverages, grams of alcohol per day was calculated from the following conversion factors and summed across the three types of alcoholic beverages: 9.6 g per medium serving of wine (3.5 fl oz), 12.0 g per medium serving of beer (12 fl oz), and 14.0 g per medium serving of liquor (1.5 fl oz).\(^2\) Our food frequency questionnaire was similar to that used in the Nurses' Health Study, which has been validated as a measure of alcohol intake.\(^2\)

Insulin concentrations (fasting and 2-hour postload) were measured by radioimmunoassay at SmithKline Laboratories (Van Nuys, Calif) using commercial kits (RSL kit for 57% of the 542 women in the present sample and Pharmacia for 43%). The lower limits of detection for the RSL and the Pharmacia kits were 5 and 3 μU/mL, respectively. Coefficients of variation for the assays ranged from 4.8% to 6.5% for a range of standards. The correlation coefficient between the two assays was 0.97, although the RSL kit tended to overestimate insulin level compared with the Pharmacia kit (Dr B. Scales, SmithKline Laboratories, personal communication). Glucose values were measured by the glucose oxidase method.\(^2\) Total HDL-C and triglycerides were determined by standardized methods at the Donnor Laboratory (Dr R. Krauss, University of California, Berkeley), a participating laboratory in the CDC lipid standardization program. After a 5-minute rest period, a mercury sphygmomanometer was used to obtain two measures each of systolic and diastolic (phase V Korotkoff sound) blood pressures, and averages of the two measures were used for data analysis. Weight was measured to the nearest 0.1 kg, and height was recorded to the nearest 0.5 cm. Body mass index (weight in kilograms/square of height in meters) was calculated as a measure of obesity. A steel measuring tape was used to obtain minimum waist girth at the natural indentation or at a level midway between the iliac crests and the lower edge of the rib cage if no natural indentation was present. Hip girth was measured at the level of the greatest protrusion of the buttocks. Girths were recorded to the nearest millimeter, and the averages of two measures (different by no more than 1 cm) were used to calculate waist-to-hip ratio and to adjust for fat distribution.

Physical activity (estimated kilocalorie expenditure per kilogram body weight per year) was assessed by an interviewer-administered questionnaire modified from the validated Coronary Artery Risk Development in Young Adults (CARDIA) instrument,\(^2\) which queried typical time spent over the past year in activities of various intensity while at home, at work, and during recreation. In addition, participants ranked their current activity level on a five-point scale relative to other women of the same age. A self-administered health history questionnaire was used to determine race, perceived health status, smoking status, medication use, menopausal status, and prior diagnosis of chronic illnesses.

Consideration of Drinkers and Abstainers

Current drinking patterns may result from either personal choice or advice in treating preexisting medical conditions or risks. Therefore, it has been suggested that never-drinkers and ex-drinkers be evaluated separately from drinkers.\(^2\) Descriptive data regarding the general health status and health-related habits of current abstainers and drinkers are shown in Table 1. Fair or poor health status was reported by more abstainers than drinkers. History of hypertension, a family history of diabetes, and obesity were each more frequent among abstainers. Physical activity level was lower

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Abstainers</th>
<th>N</th>
<th>%</th>
<th>Drinkers</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent/poor</td>
<td>117</td>
<td>86.0</td>
<td>386</td>
<td>95.1</td>
<td>136</td>
<td>25.1</td>
</tr>
<tr>
<td>Fair/poor</td>
<td>19</td>
<td>14.0</td>
<td>20</td>
<td>4.9*</td>
<td>136</td>
<td>25.1</td>
</tr>
<tr>
<td>Physician-diagnosed hypertension</td>
<td>36</td>
<td>26.5</td>
<td>86</td>
<td>21.2</td>
<td>136</td>
<td>25.1</td>
</tr>
<tr>
<td>Family history of diabetes</td>
<td>28</td>
<td>20.6</td>
<td>56</td>
<td>13.8</td>
<td>136</td>
<td>25.1</td>
</tr>
<tr>
<td>Obesity (body mass index ≥26)</td>
<td>59</td>
<td>43.4</td>
<td>97</td>
<td>23.9†</td>
<td>136</td>
<td>25.1</td>
</tr>
<tr>
<td>Current activity level</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>61</td>
<td>44.9</td>
<td>230</td>
<td>56.7</td>
<td>136</td>
<td>25.1</td>
</tr>
<tr>
<td>Moderate</td>
<td>35</td>
<td>25.7</td>
<td>89</td>
<td>22.0</td>
<td>136</td>
<td>25.1</td>
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<tr>
<td>Low</td>
<td>40</td>
<td>29.4</td>
<td>86</td>
<td>21.2*</td>
<td>136</td>
<td>25.1</td>
</tr>
<tr>
<td>Cigarette smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>12</td>
<td>8.8</td>
<td>74</td>
<td>18.2</td>
<td>136</td>
<td>25.1</td>
</tr>
<tr>
<td>Ever smokers who have quit</td>
<td>32</td>
<td>22.7</td>
<td>131</td>
<td>63.9†</td>
<td>136</td>
<td>25.1</td>
</tr>
</tbody>
</table>

*P<.05, †P<.01, ‡P<.0001 for distribution of the characteristic between abstainers and drinkers.

among these women. On the other hand, a smaller proportion of abstainers currently smoked, and a larger proportion of ever smokers had quit. Similar patterns were observed within age strata (data not shown). Because these descriptive data suggest that abstainers in this sample may be less healthy and may have changed health-related behaviors differently than drinkers, these groups of women were considered separately in analyses.

Statistical Methods

To adjust for possible differences in insulin levels determined by the RSL compared with the Pharmacia radioimmunoassay kits, all insulin data were adjusted for the assay method by use of a two-level indicator variable in regression analyses for twin data as described below.

For descriptive purposes, alcohol intake was categorized by four levels: abstainers, intake up to 1.9 g/d, 2.0 to 9.9 g/d, and ≥10 g/d. Then, among women who reported current alcohol use, alcohol intake was evaluated as a continuous variable in multiple regression models used to adjust for total caloric intake, body weight, height, waist circumference, hip circumference, family history of diabetes, and other potential confounders of the associations of alcohol intake with insulin and other outcome variables.

As a result of both genetic and environmental influences, characteristics of twins are not independently determined. Consequently, the error terms in regression models tend to be correlated within twin pairs, which generally leads to underestimated standard errors and overstated statistical significance. To adjust for the nonindependence of twins in analyses of binary outcomes (Table 1), generalized estimating equations were used. Regression analyses used generalized least-squares models with an iterative adjustment for the correlation of errors within twin pairs. This approach was extended by one of us (C.P.Q.) to allow for separate adjustment of correlated errors for each zygosity within the same model.

Because of their skewed distributions, the natural log transformations of the dependent variables fasting insulin, postload insulin, and triglycerides were used. Interpretation of the resultant β-coefficients in terms of difference in the untransformed outcome variable is calculated as percent difference using the equation  

\[ \text{percent difference} = \left(\frac{\text{abstainers} - \text{drinkers}}{\text{abstainers}}\right) \times 100 \]

Several behavioral variables have previously been related to outcome variables of interest in the present study and could confound the findings shown here. In particular, insulin levels have been related to increased dietary fat intake and decreased physical activity. The possibility of confounding was evaluated for dietary fat, physical activity, treadmill duration, cigarette smoking, use of estrogen replacement therapy, coffee drinking, and (for blood pressure models only) dietary calcium, potassium, and sodium. Those that were related to both alcohol intake and the outcome of interest were included in multiple regression models.

Analyses were then restricted to the identical twin pairs. The multiple linear regression models were repeated using intrapair differences (twin 1 value−twin 2 value) for the dependent and the independent variables. In genetically identical monozygotic twins, the matched analyses control completely for genetic influences as well as for environmental influences shared by twins. The resulting squared partial correlation coefficient is interpreted as an estimate of the proportion of nongenetic variability in the outcome measure that is accounted for by the specified independent variable. All analyses were performed with the SAS statistical computing package.

Results

The average age of the 542 women was 51 years (range, 30 to 84 years), and 92% were white. Of the sample, 25% reported no alcohol intake during the previous month. The range of alcohol consumption among the remaining 406 women was 0.3 to 77.6 g/d, and the median intake was 4.1 g/d. Assuming 12 g alcohol per drink, 37% of drinkers consumed an average of less than one drink per week, 59% took between one drink per week and two drinks per day, and 4% took three or more drinks per day.

Insulin and Other Cardiovascular Disease Risk Factors by Category of Alcohol Intake

The unadjusted mean levels of both fasting and postload insulin were lower among women who reported higher alcohol intake (Table 2). The greatest differences between successive categories of drinking occurred for nondrinkers compared with light drinkers. Generally, for the other cardiovascular disease risk factors, nondrinkers had similar or higher risk factor levels compared with current drinkers (Table 2). Because of the potential for bias when never-drinkers and ex-drinkers are combined, subsequent analyses were restricted to women who reported use of alcoholic beverages within the past month. Age-adjusted partial
correlation coefficients among variables of interest are shown in Table 3 for the 346 current drinkers.

Adjusted Associations of Alcohol Intake With Insulin and Other Variables Among Women Who Currently Drink

Table 4 shows the results of regression models for alcohol intake in relation to insulin and glucose concentrations among the individuals and the subsample of identical twin pairs who consumed alcohol during the previous month. Inverse associations were observed between alcohol intake and fasting insulin levels that were statistically significant only in the full sample ($P=.01$ and $P=.20$ for the full sample and the subset of identical twin pairs, respectively). Alcohol intake was consistently significantly inversely associated with postload insulin concentration ($P<.01$ both in the full sample of individuals and in the subset of identical twin pairs). With genetic influences removed by the matched analysis of monzygotic twin pairs, an intrapair differ-

### Table 2. Insulin Concentrations and Selected Cardiovascular Disease Risk Factors by Category of Alcohol Intake: Kaiser Permanente Women Twins Study, Second Examination, 1989-1990

<table>
<thead>
<tr>
<th>Category of Alcohol Intake (g/d)</th>
<th>Range: Median:</th>
<th>None (0 drinks)</th>
<th>0.3 to 1.9 (2 drinks per month)</th>
<th>2.0 to 9.9 (3 drinks per week)</th>
<th>10 or more (1.5 drinks per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Fasting insulin, μU/mL*</td>
<td>14.4</td>
<td>9.9</td>
<td>11.7</td>
<td>9.4</td>
<td>10.1</td>
</tr>
<tr>
<td>2-H insulin, μU/mL†</td>
<td>68.5</td>
<td>54.9</td>
<td>48.4</td>
<td>33.2</td>
<td>46.9</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>88.1</td>
<td>9.2</td>
<td>87.5</td>
<td>9.7</td>
<td>87.0</td>
</tr>
<tr>
<td>2-H glucose, mg/dL†</td>
<td>101.2</td>
<td>28.8</td>
<td>97.4</td>
<td>30.8</td>
<td>96.9</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>61.1</td>
<td>16.5</td>
<td>61.1</td>
<td>14.0</td>
<td>66.8</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>106.3</td>
<td>67.5</td>
<td>92.6</td>
<td>47.5</td>
<td>93.4</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>119.6</td>
<td>20.9</td>
<td>118.1</td>
<td>19.3</td>
<td>113.8</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>70.2</td>
<td>11.7</td>
<td>67.8</td>
<td>12.9</td>
<td>64.6</td>
</tr>
<tr>
<td>Body mass index†</td>
<td>27.1</td>
<td>7.1</td>
<td>24.9</td>
<td>5.3</td>
<td>23.7</td>
</tr>
<tr>
<td>Waist-to-hip ratio†</td>
<td>0.80</td>
<td>0.09</td>
<td>0.87</td>
<td>0.07</td>
<td>0.77</td>
</tr>
</tbody>
</table>

HDL-C indicates high-density lipoprotein cholesterol and BP, blood pressure.

*Levels of fasting and postload insulin (μU/mL), adjusted for the insulin assay kit, were 11.3, 9.9, 9.1, 9.0 and 49.5, 39.1, 38.6, 35.5, respectively, for the four categories of alcohol intake.

†For 2-hour insulin, n=532; 2-hour glucose, n=530; body mass index and waist-to-hip ratio, n=541

‡$P<.05$, §$P<.01$, ¶$P<.0001$ for comparison with light drinkers (0.3 to 1.9 g/d).

### Table 3. Age-Adjusted Partial Correlation Coefficients Between Insulin Levels and Other Variables Among Women Who Currently Drink*: Kaiser Permanente Women Twins Study, Second Examination, 1989-1990

<table>
<thead>
<tr>
<th>Dependent Variables</th>
<th>Ln Fasting Insulin</th>
<th>Ln Postload Insulin</th>
<th>Fasting Glucose</th>
<th>Postload Glucose</th>
<th>HDL-C</th>
<th>Ln TG</th>
<th>SBP</th>
<th>DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ln postload insulin</td>
<td>0.39</td>
<td>0.23</td>
<td>0.18</td>
<td>0.18</td>
<td>0.28</td>
<td>0.38</td>
<td>0.15</td>
<td>0.16</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>0.23</td>
<td>0.23</td>
<td>0.18</td>
<td>0.18</td>
<td>-0.23</td>
<td>0.38</td>
<td>0.15</td>
<td>0.16</td>
</tr>
<tr>
<td>Postload glucose</td>
<td>-0.23</td>
<td>-0.23</td>
<td>-0.07</td>
<td>-0.07</td>
<td>-0.10</td>
<td>-0.07</td>
<td>-0.10</td>
<td>-0.10</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.38</td>
<td>0.35</td>
<td>0.17</td>
<td>0.27</td>
<td>-0.37</td>
<td>0.17</td>
<td>0.22</td>
<td>0.55</td>
</tr>
<tr>
<td>Ln TG</td>
<td>0.15</td>
<td>0.19</td>
<td>0.12</td>
<td>0.21</td>
<td>-0.10</td>
<td>0.17</td>
<td>0.22</td>
<td>0.55</td>
</tr>
<tr>
<td>SBP</td>
<td>0.16</td>
<td>0.20</td>
<td>0.09</td>
<td>0.13</td>
<td>-0.09</td>
<td>0.22</td>
<td>0.22</td>
<td>0.02</td>
</tr>
<tr>
<td>DBP</td>
<td>0.09</td>
<td>0.12</td>
<td>0.14</td>
<td>-0.03</td>
<td>0.26</td>
<td>-0.02</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>Alcohol use, g/d</td>
<td>-0.09</td>
<td>-0.12</td>
<td>0.14</td>
<td>-0.03</td>
<td>0.26</td>
<td>-0.02</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>BMI</td>
<td>0.55</td>
<td>0.36</td>
<td>0.25</td>
<td>0.25</td>
<td>-0.33</td>
<td>0.45</td>
<td>0.20</td>
<td>0.22</td>
</tr>
<tr>
<td>WHR</td>
<td>0.40</td>
<td>0.35</td>
<td>0.28</td>
<td>0.28</td>
<td>-0.36</td>
<td>0.39</td>
<td>0.20</td>
<td>0.20</td>
</tr>
</tbody>
</table>

HDL-C indicates high-density lipoprotein cholesterol (mg/dL); TG, triglycerides (mg/dL); SBP, systolic blood pressure (mm Hg); DBP, diastolic blood pressure (mm Hg); BMI, body mass index; and WHR, waist-to-hip ratio. Unit of measure for glucose levels is mg/dL and for insulin levels, μU/mL.

*For analyses that include insulin levels (fasting or postload), correlation coefficients are also adjusted for the insulin assay kit. For analyses that include postload insulin or postload glucose, n=341; all others, n=346.
ence of 12 g/d alcohol (about 1 drink) was associated with a 12.4% decrement in postload insulin concentration. From this model, approximately 9% of the non-genetic variability in postload insulin was explained by alcohol consumption. These inverse associations of alcohol intake with insulin levels were also independent of HDL-C and triglyceride levels.

Adjusted analyses also revealed statistically significant inverse associations between alcohol intake and postload glucose concentrations (Table 4). Independent of genetic influences, 12 g/d alcohol was associated with a 7.2-mg/dL lower postload glucose level. Fasting glucose was not significantly related to alcohol consumption in either the matched or the unmatched models.

Alcohol consumption was directly related to HDL-C and was inversely related to triglycerides in both the unmatched models and the matched models (Table 5, \(P \leq 0.06\)). The addition of postload insulin to the models reduced the \(\beta\)-estimate for the association of alcohol intake with triglycerides by approximately one third in the unmatched model, but results were essentially unchanged in analyses of HDL-C and in the matched-pair models for triglycerides.

Alcohol intake was not associated with either systolic or diastolic blood pressure in the whole sample of current drinkers (Table 5) or among the subset of women who were not taking antihypertensive medications and with no history of physician-diagnosed hypertension (models not shown).

The current drinkers were categorized according to number of components of the insulin resistance syndrome for which the components included (1) postload insulin level above the 75th percentile for the sample (58.0 \(\mu U/mL\)), (2) triglycerides >250 mg/dL, (3) HDL-C <45 mg/dL, (4) systolic blood pressure >160 mm Hg or current use of medication for high blood pressure, and (5) waist-to-hip ratio above the 75th percentile of the sample (0.81). Alcohol intake was not related to number of components of the insulin resistance syndrome (data not shown).

Of the behavioral variables evaluated as potential confounders, only recreational activity (included in models for HDL-C) appreciably altered estimates of the associations between alcohol intake and the dependent variables, so the simpler models were presented. Adjustment for obesity and fat distribution using body mass index and waist-to-hip ratio also did not alter the findings. Analyses restricted to women who had never smoked yielded similar findings (data not shown). Analyses shown in Tables 4 and 5 were repeated excluding the 35 current drinkers who had impaired glucose tolerance, and findings were nearly identical.

### Table 4. Associations* of Alcohol Intake With Insulin and Glucose Concentrations Among Women Who Currently Drink: Kaiser Permanente Women Twins Study, Second Examination, 1989-1990

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Unmatched MZ and DZ</th>
<th>Matched Pairs, MZ only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Women</td>
<td>(\beta)</td>
</tr>
<tr>
<td>Log fasting insulin adjusted for lipid†</td>
<td>346</td>
<td>-0.004</td>
</tr>
<tr>
<td></td>
<td>346</td>
<td>-0.003</td>
</tr>
<tr>
<td>Log 2-h insulin adjusted for lipid†</td>
<td>338</td>
<td>-0.007</td>
</tr>
<tr>
<td></td>
<td>338</td>
<td>-0.007</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>346</td>
<td>0.053</td>
</tr>
<tr>
<td>2-H glucose</td>
<td>338</td>
<td>-0.227</td>
</tr>
</tbody>
</table>

MZ indicates monozygotic and DZ, dizygotic.
* All models were adjusted for weight, height, waist circumference, hip circumference, total daily caloric intake, age, and diabetes, and for models including insulin levels, the insulin assay kit. Alcohol intake levels are in g/d.
† Also adjusted for high-density lipoprotein cholesterol and triglycerides.

### Table 5. Associations* of Alcohol Intake With High-Density Lipoprotein Cholesterol, Triglycerides, and Blood Pressure Among Women Who Currently Drink: Kaiser Permanente Women Twins Study, Second Examination, 1989-1990

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Unmatched MZ and DZ</th>
<th>Matched pairs MZ only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Women</td>
<td>(\beta)</td>
</tr>
<tr>
<td>HDL-C, mg/dL adjusted for 2-h insulin</td>
<td>344</td>
<td>0.363</td>
</tr>
<tr>
<td></td>
<td>336</td>
<td>0.393</td>
</tr>
<tr>
<td>Log TG, mg/dL adjusted for 2-h insulin</td>
<td>346</td>
<td>-0.003</td>
</tr>
<tr>
<td></td>
<td>338</td>
<td>-0.002</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>346</td>
<td>-0.010</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>346</td>
<td>0.018</td>
</tr>
</tbody>
</table>

MZ indicates monozygotic; DZ dizygotic; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; and BP, blood pressure.
* All models were adjusted for weight, height, waist circumference, hip circumference, total daily caloric intake, and age. The models for HDL-C were also adjusted for recreational activity. Models that include 2-h insulin were also adjusted for the insulin assay kit.
Discussion

Among nondiabetic women who drank alcoholic beverages in the previous month, higher alcohol consumption was associated with lower concentrations of fasting and postload insulin, postload glucose, and triglycerides and with higher levels of high-density lipoprotein cholesterol. These findings were statistically significant and independent of body mass index, waist-to-hip ratio, age, and a number of other potential confounders. Associations of alcohol consumption with lipid levels were also independent of insulin concentrations. Within the limited range of alcohol intake reported by these women, there was no evidence for a large effect of alcohol on fasting glycemia or on blood pressure.

Evidence exists for genetic influences on insulin concentrations, insulin resistance, and on HDL-C, triglycerides, and liability for alcoholism. Therefore, it is possible that findings of associations between these traits may be influenced by those genetic effects. The matched analyses of monozygotic twin pairs allowed us to confirm the potential importance of behavioral variation in alcohol consumption, free from potentially confounding genetic influences.

Acute and Chronic Effects of Alcohol on Insulin and Glucose Metabolism

Insulin secretion is acutely enhanced by alcohol in the presence of other secretory stimuli, such as glucose. Oxidation of alcohol in the liver leads to reduced levels of circulating free fatty acids and to reduced gluconeogenesis; however, compensatory glycogenolysis may occur, so that hepatic glucose output and fasting glycemia may be essentially unaffected by alcohol intake. Acute hyperinsulinemia followed by relative hypoinsulinemia and/or hypoglycemia after alcohol ingestion has been reported. Other studies have shown either no effect of alcohol on insulin or glucose response to a glucose challenge or worsened glucose tolerance with alcohol ingestion. Differences in alcohol doses and mode of administration (intravenous or by mouth) may have contributed to the discrepant findings. In a comparison of "low" alcohol (about two drinks), "moderate" alcohol (about six drinks), and acetate, the "moderate" alcohol dose induced insulin resistance as measured by hyperinsulinemic clamp studies, but this effect was not observed for the low alcohol dose or for acetate.

Little is known about the relation of usual alcohol consumption with insulin concentrations or insulin resistance in populations. To the extent that both fasting and postload insulin levels can be used as surrogate measures of insulin sensitivity, our finding of an inverse relation between usual alcohol intake and insulin concentrations is consistent with results from the CARDIA study. In our data, the inverse association of alcohol consumption with fasting insulin was weaker than that for postload insulin and failed to reach statistical significance in the matched-pair analyses. This may be simply a result of the smaller sample size of this study compared with CARDIA, particularly for the matched-pair analyses. Also, Hollenbeck et al have shown post-glucose-load insulin levels to be more highly correlated with insulin-stimulated glucose uptake than fasting levels. Therefore, if light to moderate alcohol consumption influences insulin sensitivity, a stronger association with the postload compared with the fasting insulin levels might be expected.

Cross-reactivity of standard radioimmunoassay methods with proinsulin also contributes to the inaccuracy of insulin levels as a surrogate of insulin resistance. However, the problem of increased ratio of proinsulin to insulin among diabetics was avoided by exclusion of diabetics from the present analyses; insulin resistance alone apparently does not alter the proinsulin-to-insulin ratio.

Inconsistencies in reported associations of alcohol intake with glucose levels and risk for NIDDM may be caused partly by differences in the amount of alcohol consumed and its assessment within various study populations. For example, risk for NIDDM was increased with alcohol consumption among men but not women in the Rancho Bernardo study; this may be partly explained by the lower alcohol intake among women compared with men. Conversely, true sex differences may exist, because risk for NIDDM was reduced even in the highest category of alcohol consumption in the Nurses' Health Study. Within the range of light to moderate drinking observed in our sample, alcohol intake was inversely related to postload glucose levels. This relation was stronger in the analysis of differences within identical twin pairs, which may reflect either removal of variation in glucose levels as a result of genetic influences or simply sampling variability.

Alcohol, HDL-C, and Triglycerides

Alcohol ingestion >60 g/d can exert an acute hypertriglyceridemic effect and may increase the synthesis of very-low-density lipoprotein (VLDL) particles. However, in response to use of alcohol over time, catabolism of triglyceride-containing VLDL particles may be enhanced via increased activity of adipose tissue lipoprotein lipase. Thus, long-term use of moderate amounts of alcohol could be associated with decreased levels of triglycerides and increased levels of HDL particles (from the products of VLDL catabolism), as seen in the present study.

This proposed pathway is consistent with the finding of higher levels of HDL-C in association with increased alcohol intake observed in the present study and by others. However, findings for triglyceride levels are not consistent and include inverse associations with alcohol (Table 5), direct associations, and no association. Because insulin resistance has been related to higher triglyceride levels and to lower HDL-C levels, in part via lipoprotein lipase, we hypothesized that insulin levels may mediate the observed associations of alcohol with triglycerides and HDL-C. However, the inverse association of alcohol with triglycerides and the direct association of alcohol with HDL-C were independent of postload insulin levels and were not attenuated by the presence of postload insulin in the matched models (Table 5).

Alcohol Intake and Multiple Components of the Insulin Resistance Syndrome

In the present study, alcohol intake was not related to the number of components of the insulin resistance syndrome present. This is consistent with the demonstrated independence of the associations of moderate...
alcohol intake with lipids and insulin levels and the lack of association with blood pressure in that the clustering of these variables would not be expected to be related to alcohol intake.

Conclusions

Since relative hyperinsulinemia may be atherogenic through a variety of possible mechanisms apart from lipoprotein metabolism or blood pressure, the finding of an independent, inverse relation of alcohol intake with insulin levels could reflect additional mechanisms by which moderate alcohol intake may lower risk for CHD. The biological mechanism for the apparent beneficial effect of a typical pattern of moderate alcohol intake on insulin levels is not yet established but may be mediated through improved insulin sensitivity. Future work should critically evaluate dose of alcohol ingestion and pattern of alcohol intake (history and usual patterns of consumption [steady intake versus “binge” drinking]) and should carefully distinguish the acute versus long-term effects of alcohol intake on insulin levels, directly measured insulin resistance, and other related cardiovascular disease risk factors.

Acknowledgments

This research was supported by National Heart, Lung, and Blood Institute grant HL-41830-03. The comments of Drs Mary-Claire King, Robert Eckel, and Ronald Krauss are gratefully acknowledged.

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Circulation. 1993;88:2190-2197
doi: 10.1161/01.CIR.88.5.2190

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