Alcohol Consumption and Risk of Cardiovascular Disease and Death in Women
Potential Mediating Mechanisms

Luc Djoussé, MD, DSc; I-Min Lee, MBBS, ScD; Julie E. Buring, ScD; J. Michael Gaziano, MD

Background—Although an association between moderate alcohol consumption and decreased cardiovascular disease (CVD) and death has been reported, limited data are available on potential mediating mechanisms. We examined the association between alcohol and CVD and death in 26,399 women and estimated the proportion of reduced risk of CVD/death explained by a series of intermediate factors.

Methods and Results—Alcohol consumption was self-reported at baseline, and CVD events and deaths were ascertained via follow-up questionnaires and medical records. Baseline levels of hemoglobin A1c, inflammatory markers, hemostatic factors, and lipids were measured. Blood pressure and hypercholesterolemia and treatment for lipids were self-reported. During a mean follow-up of 12.2 years, 1,039 CVD events and 785 deaths (153 CVD deaths) occurred. There was a J-shaped relation between alcohol consumption and incident CVD and total and CVD deaths in a multivariable model. Compared with abstainers, alcohol intake of 5 to 14.9 g/d was associated with 26%, 35%, and 51% lower risk of CVD, total death, and CVD death, respectively, in a multivariable model. For CVD risk reduction, lipids made the largest contribution to the lower risk of CVD (28.7%), followed by hemoglobin A1c/diabetes (25.3%), inflammatory/hemostatic factors (5%), and blood pressure factors (4.6%). All these mediating factors together explained 86.3%, 18.7%, and 21.8% of the observed lower risk of CVD, total death, and CVD death, respectively.

Conclusions—These data suggest that alcohol effects on lipids and insulin sensitivity may account for a large proportion of the lower risk of CVD/death observed with moderate drinking under the assumption that the alcohol-CVD association is causal. (Circulation. 2009;120:237-244.)

Key Words: alcohol • epidemiology • cardiovascular diseases

Several epidemiological studies have reported U- or J-shaped relations between alcohol consumption and cardiovascular disease (CVD)1–5 and death.6–8 A high-density lipoprotein (HDL)—increasing effect of alcohol drinking has been demonstrated in both observational9 and intervention studies.10,11 Criqui et al12 first reported that approximately half of the protective effect of alcohol on rates of coronary disease and CVD death was mediated by HDL in a comprehensive assessment. These findings were confirmed later by other investigators9,13,14 or for a similar end point of nonfatal myocardial infarction. Although health benefits of moderate drinking (≈1 drink per day for women and 1 to 2 drinks per day for men)15 may be mediated through HDL and non-HDL factors, such as insulin sensitivity, inflammatory markers, hemostatic factors, or adiponectin,16–20 investigation of non-HDL mediators of alcohol on CVD has received limited attention, especially with incident CVD or total/CVD death as end points. In addition, limited data are available on the joint influence of major mediators of moderate drinking on death and CVD. In a nested case-control study from the Nurses Health Study and the Health Professionals Follow-Up Study, Mukamal et al21 demonstrated that alcohol consumption (at least 3 to 4 days per week) was associated with a lower risk of myocardial infarction in both sexes and that such relation was mediated by HDL, fibrinogen, and hemoglobin A1c.

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Because alcohol consumption, even in moderate ranges, may be associated with adverse health effects including raising blood pressure22,23 or increased risk of breast cancer,24,25 it is important to understand the net contribution of physiological effects of alcohol consumption on total rate of death as well as CVD. Because most of the published mediation studies have concentrated on coronary artery dis-
ease⁹,¹⁴,²¹,²⁶ and only few have focused on total CVD or all-cause and CVD death.¹²,¹³ the current project sought to examine the association between alcohol consumption and CVD and death and determine the proportion of risk reduction explained by a series of potential mediating factors in the Women’s Health Study (WHS).

**Methods**

**Study Population**

We used data from the WHS; a detailed description of the WHS has been published previously.²⁷,²⁸ Briefly, a total of 39 876 female health professionals aged 45 years and older at entry (1992–1995) were randomized to low-dose aspirin, vitamin E, or their corresponding placebos.²⁷,²⁸ Each participant gave written informed consent, and the Institutional Review Board at Brigham and Women’s Hospital approved both study protocols.

For the present analyses, we included only 28 345 women (71.1%) who provided a blood sample at baseline. We then excluded women with (1) missing data on biomarkers (n=738), (2) missing alcohol information (n=6), (3) prerrandomization reports of CVD that occurred before baseline (n=7), and (4) missing data on potential confounders, including body mass index, exercise, smoking, energy intake, fruits and vegetables, systolic blood pressure, and hypertension (n=1195). Thus a total sample of 26 399 women was used for current analyses. Characteristics between subjects who provided blood samples and those who did not were comparable (data not shown).

**Alcohol Consumption**

Alcohol consumption during the preceding 12 months was assessed by a questionnaire. Total alcohol intake was computed as the sum of the alcohol content in beer, wine, and spirits. We assumed that 360 mL (12 ounces) of beer contains 13.2 g of ethanol, 360 mL (12 ounces) of light beer contains 11.3 g of ethanol; 120 mL (4 ounces) of wine contains 10.8 g of ethanol, and 45 mL (1.5 ounces) of liquor contains 15.1 g of ethanol. Additional details on alcohol assessment in the WHS have been published.²⁹

**Ascertainment of Cardiovascular Events and Death Rates**

Detailed description of ascertainment of CVD and death rates in the WHS has been published.²⁹ Briefly, for all cases of myocardial infarction, stroke, coronary revascularization and angioplasty, or cardiovascular death reported after enrollment, hospital records were obtained and reviewed by an End Point Committee. Myocardial infarction was confirmed if symptoms met World Health Organization criteria and the event was associated with elevated cardiac enzymes or characteristic ECG changes. Each stroke case was confirmed if the patients had a new neurological deficit with signs and symptoms persisting for >24 hours (computed tomography scans were available in most cases). Revascularization procedures and angioplasty were confirmed by hospital records. Deaths were confirmed by autopsy reports, death certificates, and circumstances of death. Incident CVD included myocardial infarction, coronary angioplasty and revascularization, ischemic stroke, and cardiovascular deaths.

**Blood Collection and Measurement of Biomarkers**

Blood samples were collected at baseline in EDTA tubes and shipped cold overnight to a core laboratory, where they were centrifuged and frozen at −170°C (vapor-phase liquid nitrogen) until analysis. Hemoglobin A1c concentration was measured by turbidimetric immunoassay in red blood cells using the Hitachi 911 Analyzer (Roche Diagnostics, Indianapolis, Ind). High-sensitivity C-reactive protein was measured using a high-sensitivity ELISA (Abbott Laboratories). Fibrinogen was measured using an immunoturbidimetric assay (Kamiya Biomedical, Seattle, Wash), and soluble intercellular adhesion molecule-1 was measured using an ELISA (R&D Systems, Minneapolis, Minn). Triglyceride levels were measured enzymatically, with correction for endogenous glycerol, using a Hitachi 917 analyzer and reagents and calibrators from Roche Diagnostics. Levels of total cholesterol and HDL were measured enzymatically on a Hitachi 911 autoanalyzer (Roche Diagnostics, Basel, Switzerland), and levels of low-density lipoprotein (LDL) were determined directly (Genzyme, Cambridge, Mass). These assays are approved for clinical use by the US Food and Drug Administration.

**Other Variables**

Demographic data were collected at baseline. In addition, information on blood pressure, history of hypertension, dyslipidemia or use of cholesterol-lowering medications, history of diabetes, menopausal status, use of hormone-replacement therapy, family history of premature myocardial infarction, smoking, and physical activity was obtained at baseline. Dietary information was obtained by a food frequency questionnaire.

**Statistical Analyses**

We classified each subject into 1 of the following categories of total alcohol consumption: 0, 0.1 to 4.9, 5.0 to 14.9, 15.0 to 29.9, and ≥30 g/d. These cut points have been used previously in alcohol analyses in the WHS and make a distinction between moderate (5.0 to 14.9 g/d, which is approximately one half to 1 standard drink per day) and heavy drinking among women (more than 2 drinks per day). We computed person-time of follow-up from baseline until the first occurrence of outcome of interest (CVD or death) or censoring date, the date of receipt of the last follow-up questionnaire. We used Cox proportional hazards models to compute multivariable adjusted hazard ratios (HRs) with corresponding 95% CIs using subjects in the lowest category of alcohol consumption as the reference group. The initial model adjusted for age, whereas the multivariable model controlled for age (continuous), body mass index (<25, 25 to 29, ≥30 kg/m²), smoking (never, former, and current smokers), physical activity (quantiles of kilocalories per week), fruit and vegetable intake (≤1, 2 to 3, 4 to 5, and ≥6 servings per day), menopausal status (pre- or postmenopause or uncertain), and family history of premature myocardial infarction. This model is subsequently referred to as the basic model. Additional adjustment for energy intake (quintiles) and other nutrients did not alter the results (data not shown), and so we did not adjust for these dietary variables in the basic model. Probability value for linear trend was obtained by fitting a continuous variable that assigned the median alcohol consumption in each alcohol category in a Cox regression model. For quadratic trend, we also added a squared term in the above model. To examine the extent to which the observed lower risk of CVD or death associated with alcohol consumption is explained by a set of potential intermediate factors, we first estimated the HR from the basic model, comparing moderate drinkers (5.0 to 14.9 g/d of alcohol, or approximately one half to 1 drink per day) to abstainers. We then estimated the same HR, adding sets of intermediate factors, 1 set at a time, to the basic model. Sets of intermediate factors included (1) blood pressure factors (systolic blood pressure and use of antihypertensive medications), (2) glucose metabolism factors (prevalent diabetes and hemoglobin A1c), (3) inflammatory/hemostatic factors (high-sensitivity C-reactive protein, soluble intercellular adhesion molecule-1, and fibrinogen), and (4) lipids (treatment for high cholesterol, HDL, LDL, triglycerides). Then, we considered the magnitude of change in the HR for the moderate drinkers compared with abstainers with and without addition of each set of intermediate factors of interest. A multivariable model that included a set of intermediate factors is referred to as the intermediate factor. A larger change in the HR toward the null implied a larger mediating effect of intermediate factors on the alcohol-related reduction in CVD or risk of death. We used a previously defined equation to calculate the proportion of CVD/death risk reduction explained by each set of intermediate factors as follows: 100% × [HR from basic model − HR from intermediate factor]/[HR from basic model − 1]. For the proportion of effect explained by a set of intermediate factors, we used the following equation that also control for confounding by other potential medi-
Alcohol and Risk of CVD and Death

During a mean follow-up of 12.2 years, 1039 new CVD events, 785 confirmed deaths, and 153 cardiovascular deaths occurred. There was a J-shaped relation between alcohol consumption and CVD risk in a multivariable model adjusting for age, body mass index, smoking, physical activity, intake of fruits and vegetables, menopausal status, and family history of premature myocardial infarction, with the lowest risk observed in women consuming 5.0 to 14.9 g/d of alcohol (HR = 0.74; 95% CI 0.61 to 0.90; Table 2). Additional adjustment for aspirin or vitamin E assignment did not alter the results. Similarly, there was a J-shaped relation between alcohol consumption and rates of total death and CVD death, with the largest effect observed in women consuming 5.0 to 14.9 g/d of alcohol (HR = 0.49, 95% CI 0.27 to 0.89 for CVD death; Table 3).

Sensitivity Analyses

The source of ethanol did not influence these findings. For example, multivariable adjusted HR for total death rate was 0.90 (95% CI 0.74 to 1.10) for moderate consumption of wine compared with abstinence from wine. Corresponding values were 0.83 (95% CI 0.66 to 1.03) for beer and 0.86 (95% CI 0.72 to 1.03) for liquor in a model that simultaneously controlled for other types of beverage. When moderate drinking was defined as 5 to 30 g/d of alcohol, similar results were observed, with adjusted HR of 0.77 (95% CI 0.64 to 0.91) for CVD, 0.71 (95% CI 0.58 to 0.87) for all deaths, and 0.57 (95% CI 0.35 to 0.94) for CVD deaths compared with abstainers. Exclusion of 54 cases of breast cancer deaths did not alter the results for total death rates (ie, HR of 0.65 [95%...
CI 0.51 to 0.82] with and 0.65 [95% CI 0.51 to 0.82] without exclusion of breast cancer deaths in women consuming 5.0 to 14.9 g/d of alcohol).

Effect of Individual Adjustment of Each of the Sets of Intermediate Factors on the Point Estimate

For the incident CVD outcome, adding a set of lipid factors or glucose metabolism to the basic model each led to the largest attenuation of the HRs (Table 2). Adding a set of inflammatory/hemostatic factors or blood pressure to the basic model had a minimal effect (Table 2). For total and CVD death analyses, adding any of the set of intermediate factors to the basic model had little influence on the HRs (Table 3).

Proportion of Alcohol-Related Reduction of CVD and Death Explained by Mediators

Although additional adjustment for all sets of intermediate factors led to a complete elimination of the association between alcohol and CVD (Table 2), no major change was observed for total death rate, and a modest attenuation of the HRs was seen for CVD death rates (Table 3). When examined as a set of risk factors, lipids factors were the largest contributors to the lower risk of CVD (28.7%), followed by diabetes/hemoglobin A1c (25.3%), inflammatory/hemostatic factors (5.0%), and blood pressure factors (4.6%) (Figure). Overall, 86.3% of the lower risk of CVD observed among moderate drinkers was explained by alcohol effects on lipids, glucose metabolism, inflammatory/hemostatic factors, and blood pressure. Nearly 20% of the reduced risk of either total or CVD death among moderate drinkers was accounted for by studied mediators, respectively, assuming a causal relation between alcohol and outcome.

Discussion

In the present large prospective study, we observed a J-shaped relation between alcohol consumption and CVD and death among women. Furthermore, we estimated that 86.3% of the lower risk of CVD observed in moderate drinkers was explained by alcohol effects on lipids, glucose metabolism, inflammatory/hemostatic factors, and blood pressure. Nearly 20% of the reduced risk of either total or CVD death among moderate drinkers was accounted for by these intermediate factors. Our findings of a lower risk of CVD and death among moderate drinkers are consistent with data from the Nurses’ Health Study, which reported a J-shaped relation between alcohol consumption and total and cardiovascular death, and other cohorts that reported beneficial effects of moderate drinking on the risk of CVD.

As shown by others, our data did not support differential associations for beer, wine, or spirits. The above interpretation of our data are only valid under the assumption that moderate drinking is causally related to CVD and death and that such causal relation may be mediated by studied factors. This is obviously a big assumption, and we are far from providing proof for such relation in the absence of large, randomized controlled trials (because of ethical reasons). It is possible that unmeasured or residual confounding could explain our findings.

Alcohol has a wide range of biological effects. In a randomized cross-over trial of 63 postmenopausal women, consumption of 30 g/d of alcohol was associated with improved insulin sensitivity and lower fasting triglycerides after 8 weeks of intervention when compared with 0 g/d of alcohol. In a trial of type 2 diabetes subjects who had previously abstained from alcohol, daily consumption of 1 alcoholic drink resulted in a reduction of fasting glucose after 30 days of intervention, and such relation was stronger in...
subjects with higher hemoglobin A1c. Other investigators have reported beneficial effects of moderate drinking on glucose metabolism. In addition to the well-established HDL-raising effects of alcohol, recent data showed that alcohol consumption has been associated with a favorable lipoprotein subclass (larger particle size and fewer atherogenic small-size LDL particles). Other studies have provided evidence in support of beneficial effects of alcohol on adiponectin, C-reactive protein, fibrinogen, and adhesion molecules. The relation between alcohol intake and blood pressure has been inconsistent, with most studies reporting an increase in blood pressure with heavy alcohol consumption.

Table 3. Rates of Total Death and Cardiovascular Death According to Alcohol Consumption After Adjustment for Sets of Potential Mediators

<table>
<thead>
<tr>
<th>Alcohol Consumption (g/d)</th>
<th>0</th>
<th>0.1–4.9</th>
<th>5.0–14.9</th>
<th>15.0–29.9</th>
<th>30.0+</th>
<th>P Trend*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>1.0</td>
<td>0.92 (0.78–1.09)</td>
<td>0.66 (0.53–0.83)</td>
<td>1.02 (0.75–1.39)</td>
<td>1.61 (1.15–2.24)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Basic model 1**</td>
<td>1.0</td>
<td>0.91 (0.77–1.07)</td>
<td>0.65 (0.51–0.82)</td>
<td>0.90 (0.66–1.23)</td>
<td>1.26 (0.90–1.77)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Basic model plus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure factors†</td>
<td>1.0</td>
<td>0.91 (0.77–1.08)</td>
<td>0.66 (0.52–0.83)</td>
<td>0.87 (0.64–1.19)</td>
<td>1.21 (0.86–1.70)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Glucose metabolism factors‡</td>
<td>1.0</td>
<td>0.94 (0.79–1.11)</td>
<td>0.68 (0.54–0.86)</td>
<td>0.93 (0.68–1.28)</td>
<td>1.33 (0.94–1.86)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Inflammatory/hemostatic factors§</td>
<td>1.0</td>
<td>0.94 (0.79–1.11)</td>
<td>0.70 (0.55–0.88)</td>
<td>0.98 (0.72–1.35)</td>
<td>1.38 (0.98–1.95)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Lipid factors‖</td>
<td>1.0</td>
<td>0.92 (0.78–1.08)</td>
<td>0.66 (0.52–0.83)</td>
<td>0.89 (0.65–1.23)</td>
<td>1.25 (0.88–1.76)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>All intermediate factors</td>
<td>1.0</td>
<td>0.96 (0.81–1.13)</td>
<td>0.72 (0.56–0.91)</td>
<td>0.95 (0.69–1.30)</td>
<td>1.33 (0.94–1.88)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>1.0</td>
<td>0.95 (0.66–1.37)</td>
<td>0.47 (0.26–0.84)</td>
<td>0.87 (0.42–1.81)</td>
<td>1.62 (0.78–3.35)</td>
<td>0.004</td>
</tr>
<tr>
<td>Basic model 1**</td>
<td>1.0</td>
<td>0.97 (0.67–1.40)</td>
<td>0.49 (0.27–0.89)</td>
<td>0.79 (0.38–1.66)</td>
<td>1.32 (0.63–2.78)</td>
<td>0.01</td>
</tr>
<tr>
<td>Basic model plus</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure factors†</td>
<td>1.0</td>
<td>0.98 (0.68–1.42)</td>
<td>0.51 (0.28–0.93)</td>
<td>0.71 (0.34–1.49)</td>
<td>1.11 (0.53–2.35)</td>
<td>0.03</td>
</tr>
<tr>
<td>Glucose metabolism factors‡</td>
<td>1.0</td>
<td>1.06 (0.73–1.54)</td>
<td>0.56 (0.30–1.02)</td>
<td>0.85 (0.40–1.79)</td>
<td>1.47 (0.69–3.12)</td>
<td>0.03</td>
</tr>
<tr>
<td>Inflammatory/hemostatic factors§</td>
<td>1.0</td>
<td>1.00 (0.69–1.44)</td>
<td>0.52 (0.28–0.94)</td>
<td>0.85 (0.40–1.76)</td>
<td>1.42 (0.68–3.02)</td>
<td>0.02</td>
</tr>
<tr>
<td>Lipid factors‖</td>
<td>1.0</td>
<td>1.02 (0.71–1.48)</td>
<td>0.54 (0.29–0.98)</td>
<td>0.84 (0.40–1.76)</td>
<td>1.44 (0.68–3.05)</td>
<td>0.03</td>
</tr>
<tr>
<td>All intermediate factors</td>
<td>1.0</td>
<td>1.07 (0.74–1.55)</td>
<td>0.60 (0.33–1.10)</td>
<td>0.84 (0.40–1.79)</td>
<td>1.37 (0.64–2.96)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Data are presented as hazard ratios (95% CIs).

*Adjusted for age (continuous), body mass index (<25, 25–29.9, ≥30 kg/m²), smoking (never, former, and current smokers of <15 and ≥15 cigarettes/d), physical activity (quintiles of kilocalories per week), fruit and vegetable intake (≤1, 2–3, 4–5, and ≥6 servings per day), menopausal status (premenopause, postmenopause, or uncertain), and family history of premature myocardial infarction (yes/no); P value for quadratic trend.

†Includes treatment for hypertension (yes/no) and systolic blood pressure (<120, 120–129, 130–139, 140–149, and ≥140 mm Hg).

‡Includes history of diabetes mellitus and hemoglobin A1c.

§Includes quintiles of high-sensitivity C-reactive protein, fibrinogen, and soluble intercellular adhesion molecules.

‖Includes quintiles of high-density and low-density lipoprotein cholesterol, triglycerides, treatment for hypercholesterolemia.

% Reduction in events

Figure. Percentage reduction in events (cardiovascular disease [CVD], total death, and CVD death) with moderate alcohol consumption (5.0 to 14.9 g/d) that is explained by a series of risk factors. The proportion explained by all intermediate factors was computed as follows: 100%×((HRbasic model−HRintermediate factors)/(HRbasic model−1)). To improve accuracy, HRs were expressed up to 5 decimal points. The independent proportion explained by a single set of mediators was computed as (HR3−HR2)/(1−HR1), where HR3 is the HR for moderate alcohol use from the model including all intermediate factors, HR2 is from the model including all but the intermediate factor of interest, and HR1 is from the basic model excluding all intermediate factors. HR indicates hazard ratio; Hb, hemoglobin.
consumption. These biological paths of alcohol intake lend support to an important role of alcohol on glucose metabolism, lipids, and inflammatory markers in explaining ≈86% of reduced risk of CVD observed in this study. This is consistent with a report showing that HDL, hemoglobin A1c, and fibrinogen explained 100% of the association between drinking and myocardial infarction in the Health Professionals Follow-Up Study and 80% of the effects observed in the Nurses’ Health Study. In both men and women, HDL alone explained approximately half of the observed association. HDL accounted for ≈50% of the lower risk of CHD observed with alcohol consumption, whereas LDL and blood pressure had minimal influences. These data are consistent with other reports of mediation of alcohol-CHD relation by HDL.

We observed a minimal attenuation of the effects of moderate drinking on CVD on control of hypertension variables. This finding is contrary to our primary hypothesis of a blood pressure–raising effect of any alcohol consumption. However, in heavy drinkers, we observed expected results in that the alcohol effect on CVD risk (17% lower risk) was greater (27% lower risk) on control of blood pressure variables (Table 2).

In the present study, 18.7% of total deaths and 21.8% of cardiovascular deaths were explained by a combination of studied intermediate factors. In the Multiple Risk Factor Intervention Trial (MRFIT), HDL explained 45% of the association between alcohol intake and the rate of CHD death in men. Consistent with our data, the Lipid Research Clinics (LRC) Follow-up Study showed that moderate drinking in men and women was associated with a lower risk for CVD death, and such relation was partially mediated by HDL and not LDL cholesterol (eg, relative risk of 0.45 without and 0.54 with additional control for HDL in women). Of note is that there were only 48 CVD deaths in the LRC study, and the study, although not showing a significant effect, was underpowered.

Contrary to the larger effect of alcohol explained by lipids, hemoglobin A1c, and inflammatory and hemostatic factors in our study, a relatively small proportion of total and CVD deaths was explained by these factors. How might we explain such difference? It is possible that some of the beneficial effects of moderate drinking on CVD could be offset by excess risk of breast cancer, as reported by others. This scenario would attenuate the proportion of total deaths explained by alcohol effects in comparison to the proportion of CVD deaths or CVD events explained by alcohol intake. However, exclusion of deaths from breast cancer did not alter the findings on total death rates, suggesting limited influence of breast cancer deaths on our findings.

In conclusion, alcohol intake and CVD risk. Alternatively, other biological mechanisms not evaluated in the present study may be responsible for the alcohol-death relation. Furthermore, difficulties assigning the true cause of death in some cases may also contribute to such difference.

The present study has some limitations. It is possible that some of the covariates examined (ie, hypertension or diabetes) may have influenced subsequent consumption of alcohol, suggesting that they could be both intermediate factors and confounders. Thus the use of alcohol and predictors of CVD assessed at a single time point does not allow to properly examine mediation in this setting, and as consequence, our estimates of the proportion of CVD explained may be biased.

Generalizability of our data is limited by the fact that participants were female health professionals who may have different behaviors than men or the general population because of their higher educational attainment and a high socioeconomic status. We had a single measurement of intermediate factors that might have been influenced by factors unrelated to alcohol intake. Self-report on alcohol intake may have led to exposure misclassification (over- or underreporting). Because of the lack of repeated measures on alcohol consumption over time, we were unable to account for change in alcohol consumption over time in this cohort. Lastly, because individuals were not randomly assigned to alcohol consumption, we cannot exclude chance, residual confounding, or confounding by unmeasured variables, including psychological factors, as a possible explanation of our findings. Nevertheless, our large sample size, the relatively long follow-up, the standardized ascertainment of CVD events and deaths in the WHS, and the availability of various covariates are major strengths of this study.

Conclusions

In conclusion, our data suggest that a large proportion of the lower risk of CVD observed with moderate drinking may be accounted for by factors related to glucose metabolism, lipids, and inflammation/hemostasis in adult women under the assumption of a causal relation between moderate drinking and CVD. If confirmed in other populations, such information may help clarify the possible mechanisms underlying the observed association between moderate alcohol intake and CVD risk.

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Disclosures

None.

References


Although an association between moderate alcohol consumption and decreased cardiovascular disease (CVD) and death has been reported, limited data are available on potential mediating mechanisms. In a prospective study of 26,399 women, we found a J-shaped association between alcohol consumption and rates of incident CVD, total death, and CVD death in a multivariable model. Compared with abstainers, moderate drinking (5 to 14.9 g/d of alcohol) was associated with 26%, 35%, and 51% lower risk of CVD, total death, and CVD death, respectively, after adjustment for major confounding factors. Under the assumption of a causal relation between moderate drinking and CVD, we estimated the individual and joint contribution of possible mediators of such relation and found that lipids made the largest contribution to the lower risk of CVD (28.7%), followed by hemoglobin A1c/diabetes (25.3%), inflammatory and hemostatic factors (5%), and blood pressure factors (4.6%). All these mediating factors together explained 86.3%, 18.7%, and 21.8% of the observed lower risk of CVD, total death, and CVD death, respectively, assuming a causal relation between alcohol and outcome. Of note is that the above interpretation is only possible under the causality assumption and does not imply proof of concept from current data. Instead, our data suggest a differential role of a potential mediator of an alcohol and CVD relation. Experimental models are warranted to confirm these hypotheses. In the absence of a definitive answer for humans, the decision on moderate drinking for individual persons should consider the potential risks associated with alcohol intake, along with global CVD risk appraisal.
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