Randomized Controlled Intervention of the Effects of Alcohol on Blood Pressure in Premenopausal Women

Trevor A. Mori, Valerie Burke, Lawrence J. Beilin, Ian B. Puddey

Abstract—Alcohol has been consistently demonstrated to elevate blood pressure (BP) in intervention studies in men. There are uncertainties, however, as to the nature of the relationship in women. We, therefore, determined in healthy premenopausal women the dose-dependent effects of alcohol on ambulatory BP. Twenty-four participants aged 25 to 49 years, with a mean alcohol intake of 202±94 g alcohol/wk and mean 24-hour systolic and diastolic BP of 110.2±8.9/68.9±5.7 mm Hg, were randomized to a 3-period cross-over study. Each evening they consumed higher volume red wine (lower level drinkers, 146 g alcohol/wk; higher level drinkers, 218 g alcohol/wk), lower volume red wine (lower level drinkers, 42 g alcohol/wk; higher level drinkers, 73 g alcohol/wk), or dealcoholized red wine, each for a period of 4 weeks. Higher volume red wine significantly increased 24 hours systolic and diastolic BP relative to dealcoholized red wine (by 2.0±0.6/1.2±0.4 mm Hg; P=0.001 and P=0.028, respectively). There were similar changes for higher volume red wine relative to lower volume red wine (by 1.6±0.6/1.4±0.4 mm Hg; P=0.014 and P=0.005, respectively). These effects were predominantly on awake rather than asleep BP. There was no significant difference in BP between lower volume red wine and dealcoholized red wine. We conclude that in healthy premenopausal women regular consumption of alcohol as 200 to 300 mL red wine/d elevates 24 hours systolic and diastolic BP. The magnitude of the increase in BP is similar to that previously reported in intervention studies in men. (Hypertension. 2015;66:00-00. DOI: 10.1161/HYPERTENSIONAHA.115.05773.) • Online Data Supplement

Key Words: alcohol drinking • blood pressure • randomized controlled trial • wine • women

After the effects of body weight, alcohol consumption is one of the strongest potentially modifiable risk factors for hypertension. Paradoxically, several cross-sectional epidemiological studies suggest that low-level alcohol consumption (4–7 drinks/wk) associates with lower blood pressure (BP) in women, with curvilinearity of the alcohol–BP relationship more marked in women compared with men. However, associations between alcohol intake and hypertension have not been as extensively evaluated in women and women are underrepresented in the heavier drinking categories in most cross-sectional studies.

The Marks and Spencer Cardiovascular Risk Study from the United Kingdom of >14000 women reported a decreased prevalence of hypertension with ≤14 drinks/wk but suggested this was largely explained by age, body mass index, physical activity, and family history of premature coronary heart disease. The National Health and Nutrition Examination Survey (NHANES) III study with >9000 women showed associations of alcohol intake with systolic BP and pulse pressure that were considerably smaller in women compared with men. A subsequent NHANES analysis confined to those drinking ≥1 drinks/d and a cross-sectional study from Spain, both showed that systolic and diastolic BP significantly associated with alcohol in men but not in women. In contrast, cross-sectional studies from Brazil and Canada showed substantially increased levels of BP in women for the same level of intake compared with men.

Prospective population studies have not resolved this controversy. The Atherosclerosis Risk in Communities (ARIC) study showed that long-term risks for developing hypertension with ≥210 g alcohol/wk were similar in men and women. The Nurses Health Study II of 70891 women aged 25 to 42 years found a biphasic effect of alcohol, with a 14% decrease in risk in those consuming 2 to 3.5 drinks/wk and a 20% increase in those drinking >14 drinks/wk. The Hisayama study from Japan showed incidence of hypertension increased 2-fold with light drinking (<23 g/d) in men but not in women. In the US-based Coronary Artery Risk Development in Young Adults (CARDIA) study, the 20-year incidence of hypertension was decreased in women at all levels of alcohol intake. A meta-analysis in 2009 identified 12 prospective studies that included 11 male and 9 female data sets. The study reported a linear relationship between alcohol and risk of hypertension for men but a modest protective effect in women drinking <15
g alcohol/d, which reached its nadir at 4 g/d (0.82 relative risk for hypertension). However, thereafter there was a linear and steeper slope in women than in men culminating in a relative risk of 2.81 at 100 g alcohol/d. A meta-analysis in 2012 of 16 prospective studies15 similarly identified a J-shaped relationship for women, but not for men, with a 0.87 relative risk for hypertension in those drinking <10 g/d. Drinking >30 g/d significantly increased the risk of hypertension in both men and women.

To our knowledge, there are no interventions confined to women that have determined the direction and magnitude of different doses of alcohol on BP. Studies to date have focused on the effects of alcohol in pre- and postmenopausal women to increase high-density lipoprotein-cholesterol (HDL-C)16,17 or to improve insulin sensitivity18 or hemostatic factors.19 We aimed to examine in premenopausal women if the consumption of 42–73 g alcohol/wk (≈4–7 standard drinks with 1 standard drink defined as containing 10 g alcohol) for 4 weeks can lower BP and if the consumption of 146–218 g alcohol/wk (≈14–21 standard drinks) for 4 weeks will increase BP, compared with a similar period of abstinence from alcohol.

Methods

Study Participants

Healthy premenopausal, nonsmoking women 20 to 45 years of age were recruited by media advertisement and community screening. Participants were regular drinkers with the same pattern of alcohol intake for ≥12 months. They had a body mass index <30 kg/m² and no history of hypertension, dyslipidemia, diabetes mellitus, liver disease, or coronary, cerebrovascular or peripheral vascular disease, and were free of clinical evidence of vascular disease on examination. They were not taking any medications, including aspirin, nonsteroidal anti-inflammatory drugs, or the oral contraceptive pill.

Study Design

During a 4-week run-in period, participants continued their usual alcohol intake. They were subdivided on the basis of their usual alcohol intake into 2 groups, lower level consumers (drinking <200 g alcohol/wk) and higher level consumers (drinking >200 g alcohol/wk). They then entered an unblinded phase of a 3-period crossover study of Latin square design, each period of 4 weeks duration (Figure S1 in the online-only Data Supplement). The 3 study periods were higher volume red wine with lower level consumers drinking 200 mL/d (≈146 g alcohol/wk) and higher level consumers drinking 300 mL/d (≈218 g alcohol/wk), a lower volume of the same red wine with lower level consumers drinking 100 mL/d on 4 days a week (≈42 g alcohol/wk) and higher level consumers drinking 100 mL/d (≈73 g alcohol/wk), and as a control an identical dealcoholized red wine that was consumed in daily volumes equivalent to those during the higher volume red wine period. During this 4-week period, they otherwise remained totally abstinent from all alcohol. The red wine was a Shiraz Cabernet blend of known composition. They were free of clinical evidence of vascular disease on examination. They were not taking any medications, including aspirin, nonsteroidal anti-inflammatory drugs, or the oral contraceptive pill.

BP Monitoring

Ambulatory BP and heart rate were monitored every 30 minutes for 24 hours at the end of each study period. A trained nurse fitted a SpaceLabs Monitor (Model 90217, SpaceLabs Medical Inc) to the nondominant arm 2-2.5 cm above the antecubital fossa and explained its use to the participants. They were instructed to continue their usual daily activities and avoid any vigorous exercise. Measurements showing a test code or those with a pulse pressure <20 mm Hg were excluded from the analysis. BP traces were considered complete if ≥80% of the recordings were valid. BP readings from each subject were aggregated to calculate average hourly results. Subjects kept a diary of when they were asleep or awake from which BP readings were further aggregated into 24 hour, awake, and asleep means.

Measurement of Compliance and Lifestyle Change

Compliance with changes in alcohol intake was recorded by 7-day retrospective diaries completed at weekly visits to the clinical trials unit. A fasting blood sample was provided at the end of the 4-week run-in period and the end of each study period for γ-glutamyl transpeptidase and HDL-C as biomarkers of change in alcohol intake, and total cholesterol, triglycerides, and low-density lipoprotein-cholesterol. Participants were advised not to change their usual dietary habits. They completed food frequency questionnaires at baseline and at the end of each study period to monitor any changes in diet or nutrient intake. Physical activity logs were completed and weight monitored at the end of run-in and the conclusion of each study period. Twenty-four hour urinary 4-O-methylgallic acid was determined as a biomarker of red wine intake.20

Biochemical Analyses

Blood was collected after an overnight fast and serum samples were analyzed by Core Laboratory Services, Royal Perth Hospital, using the Hitachi 917 Biochemical Analyser (Hitachi Limited, Tokyo, Japan). γ-Glutamyl transpeptidase was measured with a Roche kit (Roche Diagnostics GmbH, D-68298, Mannheim, Germany). HDL-C was measured with the Boehringer Mannheim kit. Low-density lipoprotein-cholesterol was calculated using the Friedewald formula. Plasma fibrinogen was assayed by the thrombin time titration method described by Clausen using a MLA electra 1600 CHD coagulation analyzer. Aliquots from 24-hour urine collections stored at −80°C were assayed for 4-O-methylgallic acid by gas chromatography–mass spectrometry.20 All samples from each subject were assayed in the 1 batch.

Statistics

The 24-hour ambulatory BP records were analyzed using repeated measures mixed models allowing for the correlated error structure in the data (Proc Mixed; Statistical Analysis Program; SAS Institute). Using the data from our previous study of the effects of beer and red wine on ambulatory BP in men,22 this study had at least 80% power to demonstrate a 2 to 3 mm Hg change in 24-hour ambulatory systolic BP. Weight, compliance biomarkers, and cardiovascular biomarkers at end of each 4-week beverage intervention were analyzed with generalized linear modeling (GLM) repeated measures using IBM SPSS Statistics Version 20 software and were considered significant with P<0.05 after Bonferroni adjustment. Baseline data are reported as mean±SD. Nonbaseline values are reported as mean±SD.

Results

There were 132 respondents by telephone screened against the entry inclusion and exclusion criteria, 57 were invited for intensive screening at the clinical trials unit. Ten would not commit to the 16-week trial, 7 would not commit to a period of abstinence or did not wish to consume a dealcoholized beverage, 9 were taking various medications, and 7 had a body mass index >30 kg/m² leaving 24 who were
randomized and all completed the study. They were aged 24 to 49 years with a mean of 39.3±7.3 years, a body mass index of 23.6±3.3 kg/m², and mean 24-hour systolic and diastolic BP of 110.2±8.9/68.9±5.7 mm Hg, respectively (Table S1). Usual alcohol intake was 202±94 g alcohol/wk. They predominantly drank wine, the majority on 5 to 7 d/wk with 2 participants drinking only on 2 to 3 d/wk. Participants were normo-lipidaemic and comprised 16 ex-smokers and 8 who had never smoked.

There was no off-protocol consumption of alcohol reported by participants during the study. Urinary 4-O-methylgallic acid as a biomarker of red wine intake was similar during the dealcoholized red wine and high volume red wine periods, but was reduced by ≈50% during the low volume red wine period (Table 1). Levels of γ-glutamyl transpeptidase were similar during all 3 study periods. High volume red wine, but not lower volume red wine significantly raised HDL-C and reduced plasma fibrinogen relative to dealcoholized red wine. There was no effect of either high or low volume red wine on serum total cholesterol, triglycerides, low-density lipoprotein-cholesterol, glucose or insulin, relative to dealcoholized red wine. Weight was ≈0.5 kg higher during the high volume red wine period while 24-hour urinary sodium excretion was unchanged throughout the study. There were no reported changes in diet or level of physical activity.

The diurnal profiles for 24-hour systolic and diastolic BP on the final day of each period are shown in Figure. Table 2 shows the mean 24-hour ambulatory, day-time and night-time systolic and diastolic BP and heart rate during the 3 study periods. Compared with dealcoholized red wine, higher volume red wine increased 24-hour systolic and diastolic BP by 2.0±0.6/1.2±0.4 mm Hg; P=0.001 and P=0.028, respectively. Compared with lower volume red wine, higher volume red wine increased both 24-hour systolic and diastolic BP by 1.6±0.6/1.4±0.4 mm Hg; P=0.014 and P=0.005, respectively. The effects were more pronounced when participants were awake (Figure; Table 2). There was no significant difference in 24-hour systolic and diastolic BP between dealcoholized red wine and lower volume red wine. There were no significant differences in ambulatory heart rate between the 3 study periods (Table 2).

### Discussion

This study demonstrates for the first time a BP-elevating effect of alcohol in premenopausal women. Awake systolic and diastolic BP were 2.3/1.3 mm Hg higher in women who consumed 146–218 g alcohol/wk (≈2–3 standard drinks/d) as red wine for 4 weeks when compared with a similar period when only dealcoholized red wine was consumed. There was no effect of lower level alcohol intake (42–73 g alcohol/wk; ≈0.5–1 standard drink/d) to lower BP.

The first meta-analysis of randomized controlled trials of the effects of alcohol reduction on BP identified 15 trials. It comprised 7 trials from our group including the first intervention studies demonstrating a direct effect of alcohol to increase BP in normotensive and treated hypertensive men and the first to assess the effects of pattern of alcohol intake on ambulatory BP. Men were the sole participants in 12 of these trials and by far the overwhelming majority in the remaining 3 trials and so a breakdown of outcomes by sex was not feasible. The median trial duration was 8 weeks and participants reduced alcohol consumption by a median 76% from a base intake of 3 to 6 standard drinks/d. The pooled effect estimate of alcohol reduction on systolic and diastolic BP was 3.3/2.0 mm Hg, respectively. This study

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**Table 1. Weight, Compliance Biomarkers, and Cardiovascular Biomarkers at End of Each 4-Week Beverage Intervention**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dealcoholized Red Wine</th>
<th>Red Wine (Lower Volume)</th>
<th>Red Wine (Higher Volume)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, kg</td>
<td>66.3±2.1†</td>
<td>66.4±2.1</td>
<td>66.9±2.1</td>
<td>0.008</td>
</tr>
<tr>
<td>γ-GT, U/L</td>
<td>16.6±3.5</td>
<td>15.4±2.2</td>
<td>16.7±2.3</td>
<td>NS</td>
</tr>
<tr>
<td>4-O-methylgallic acid, μg/d</td>
<td>501±71†§</td>
<td>255±48†</td>
<td>502±96</td>
<td>0.006</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>4.68±0.18</td>
<td>4.63±0.16</td>
<td>4.77±0.14</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>0.86±0.06</td>
<td>0.81±0.04</td>
<td>0.84±0.04</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-cholesterol, mmol/L</td>
<td>1.79±0.08*§</td>
<td>1.84±0.08§</td>
<td>1.97±0.09</td>
<td>0.013</td>
</tr>
<tr>
<td>LDL-cholesterol, mmol/L</td>
<td>2.50±0.17</td>
<td>2.42±0.16</td>
<td>2.42±0.12</td>
<td>NS</td>
</tr>
<tr>
<td>Fibrinogen, mmol/L</td>
<td>3.15±0.12*§</td>
<td>2.97±0.13</td>
<td>2.71±0.09</td>
<td>0.007</td>
</tr>
<tr>
<td>Urinary sodium, mmol/24 h</td>
<td>128±10</td>
<td>112±7</td>
<td>140±11</td>
<td>NS</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>4.20±0.10</td>
<td>4.31±0.08</td>
<td>4.17±0.08</td>
<td>NS</td>
</tr>
<tr>
<td>Insulin, mU/L</td>
<td>5.44±0.58</td>
<td>5.21±0.55</td>
<td>5.88±0.57</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data represent mean±SE. GT indicates glutamyl transpeptidase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and NS, nonsignificant.

*Red wine (higher volume), †red wine (lower volume). Generalized linear modeling (GLM) repeated measures used with post hoc analysis by modified t test with Bonferroni correction (†P<0.05, §P<0.01).
now confirms for the first time a similar BP-raising effect of alcohol in premenopausal women who consumed ≈ 2 to 3 standard drinks/d as red wine for 4 weeks compared with a period of abstinence. However, the change in BP with alcohol in our intervention was less than the predicted estimates from the large cross-sectional Intersalt study, where in women consuming >300 mL alcohol/wk (≥34 g alcohol/d) systolic and diastolic BP were 3.9/3.1 mm Hg higher than in nondrinkers. This is likely a reflection of a relatively lower overall alcohol intake during our intervention. Evidence of a dose–response relationship between the falls in BP and the reduction in alcohol intake was seen in the previously cited meta-analysis.

Intervention studies in women that in contrast to our findings detected no BP-elevating effect of alcohol used lower volumes of red wine or did not have BP as the primary end point and usually also included men. In a cross-over trial from the United States in 20 overweight middle-aged normotensive premenopausal women, 270 mL red wine/d (28.1 g alcohol) for 5 days a week for 10 weeks had no effect on BP relative to a period of abstinence. A parallel designed intervention study from Denmark with 69 healthy 38 to 74 year old men and women randomized to 300 mL red wine/d (38.3 g alcohol) or 200 mL red wine/d (25.5 g alcohol), or grape extract tablets at 1 of 2 doses for 4 weeks, showed no significant effects on BP relative to water. Similarly, there were no significant effects on BP in a parallel design intervention study from Luxembourg that included 108 men and women with carotid atherosclerosis consuming either 300 or 200 mL red wine/d, or no alcohol as a control, for 20 weeks. It is noteworthy that in 2 of these studies, clinic BP was measured using standard sphygmomanometry rather than 24-hour ambulatory BP. The third study analyzed the mean 24-hour ambulatory BP rather than using repeated measures models for the entire 24-hour BP curve as in this study.

In our study, a low-level intake of red wine (≈42–73 g alcohol/wk) had no effect on BP relative to dealcoholized red wine, suggesting that the reduced BP seen in some cross-sectional and longitudinal population studies in women is

### Table 2. Results From 24-h Ambulatory BP Conducted at the End of Each 4-Week Beverage Intervention

<table>
<thead>
<tr>
<th>BP and Heart Rate</th>
<th>Red Wine (HV)</th>
<th>Red Wine (LV)</th>
<th>Dealcoholized Red Wine</th>
<th>Change in BP and Heart Rate</th>
<th>Red Wine (HV) vs Dealcoholized Red Wine</th>
<th>Red Wine (LV) vs Dealcoholized Red Wine</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-h SBP</td>
<td>108.9±0.4</td>
<td>107.3±0.4</td>
<td>106.9±0.4</td>
<td>1.6±0.6*</td>
<td>2.0±0.6†</td>
<td>0.4±0.6†</td>
</tr>
<tr>
<td>Awake SBP</td>
<td>115.3±0.5</td>
<td>113.3±0.5</td>
<td>113.1±0.5</td>
<td>2.0±0.7*</td>
<td>2.3±0.7‡</td>
<td>0.2±0.7‡</td>
</tr>
<tr>
<td>Asleep SBP</td>
<td>97.0±0.6</td>
<td>96.2±0.6</td>
<td>95.8±0.6</td>
<td>0.8±0.9</td>
<td>1.2±0.9</td>
<td>0.4±0.8</td>
</tr>
<tr>
<td>24-h DBP</td>
<td>68.4±0.3</td>
<td>67.0±0.3</td>
<td>67.3±0.3</td>
<td>1.4±0.4‡</td>
<td>1.2±0.4*</td>
<td>−0.3±0.4</td>
</tr>
<tr>
<td>Awake DBP</td>
<td>73.9±0.4</td>
<td>72.1±0.4</td>
<td>72.6±0.4</td>
<td>1.8±0.5‡</td>
<td>1.3±0.5§</td>
<td>−0.5±0.5</td>
</tr>
<tr>
<td>Asleep DBP</td>
<td>58.3±0.5</td>
<td>57.6±0.5</td>
<td>57.8±0.5</td>
<td>0.7±0.7</td>
<td>0.5±0.6</td>
<td>−0.2±0.6</td>
</tr>
<tr>
<td>24-h HR</td>
<td>73.8±0.4</td>
<td>74.5±0.4</td>
<td>74.4±0.9</td>
<td>−0.7±0.6</td>
<td>0.6±0.6</td>
<td>−0.02±0.6</td>
</tr>
<tr>
<td>Awake HR</td>
<td>77.9±0.6</td>
<td>79.0±0.6</td>
<td>79.7±0.6</td>
<td>−1.1±0.8</td>
<td>−1.8±0.8</td>
<td>−0.7±0.8</td>
</tr>
<tr>
<td>Asleep HR</td>
<td>66.5±0.5</td>
<td>66.0±0.6</td>
<td>65.2±0.5</td>
<td>0.5±0.8</td>
<td>1.3±0.8</td>
<td>0.8±0.8</td>
</tr>
</tbody>
</table>

*Data are mean±SE. BP indicates blood pressure; DBP, diastolic BP (mm Hg); HR, heart rate (beats per minute); HV, higher volume; LV, lower volume; and SBP, systolic BP. Pairwise comparison of estimated marginal means from mixed model analysis
*P<0.05, †P<0.001, ‡P<0.01, and §P=0.057.
more likely because of the presence of unmeasured confounders. The case for such unmeasured confounding is strengthened by the observation in the Behavioural Risk Factor Surveillance System Survey, a telephone survey of >200,000 adults in the United States, that 27 of 30 cardiovascular-associated risk factors were significantly more prevalent in nondrinkers than in light-to-moderate drinkers. The authors suggested that in using nondrinkers as the comparison group in any studies of the effects of alcohol on cardiovascular risk, the presence of a large number of unmeasured effect-modifiers may inflate the perception of any perceived benefits from drinking. It is likely that potential differences in major unmeasured effect-modifiers between men and women could include pattern of drinking, dietary intake, patterns of adiposity, and levels of physical activity.

Unmeasured confounding in epidemiological surveys may have also arisen from sex differences in drinking behavior. A large cross-sectional US survey of >19,000 participants found that women with a previous diagnosis of hypertension consumed significantly less alcohol than women who did not report hypertension. In contrast, self-reported hypertensive men consumed equal or greater amounts of alcohol than self-reported normotensive men. Such sex differences in drinking behavior despite knowledge of higher BP may well have biased cross-sectional surveys that have suggested an influence of sex on the alcohol–BP relationship.

Several prospective studies have identified lower risks for both total and cardiovascular mortality with mild-to-moderate alcohol consumption in women, including those with hypertension. Lower BP or a decreased risk of hypertension have been implicated in these studies as potential mediating mechanisms for the decrease in risk, albeit relatively weakly when compared with the benefits of alcohol in raising HDL-C and improving insulin sensitivity, inflammatory markers, and hemostatic factors. The results of this intervention study, however, do not support a BP-lowering effect of alcohol as a contributor to lower cardiovascular risk with mild-to-moderate drinking in women. On the contrary, they suggest that at higher levels of alcohol intake any beneficial effects could be mitigated by an increase in BP. That said, although the higher dose of alcohol in our study increased BP, it also significantly raised HDL-C by ≈10% and reduced fibrinogen levels by ≈14%. These changes are consistent with data from a meta-analysis that concluded the increase in HDL-C and the fall in fibrinogen with 2 to 3 drinks/d could substantially decrease coronary artery disease risk. Previous reports have suggested a 10% increase in HDL-C as observed with moderate alcohol consumption could translate into a 10% to 13% decrease in coronary artery disease risk in postmenopausal women and ≤25% in premenopausal women. However, such estimates have not accounted for the potential influence of any corresponding detrimental increases in BP or doubts as to whether HDL-C is an important mediator of the decrease in risk of coronary artery disease with increasing alcohol intake.

There have been consistent suggestions that the regular consumption of red wine should lower BP, a concept fuelled by animal studies demonstrating vasodilator and antihypertensive effects of polyphenolic compounds in red wine. However, population-based studies have indicated an increase in BP with beer, wine, or spirits. We have demonstrated in a controlled trial in men that 24-hour ambulatory BP increased similarly after 4 weeks of consuming red wine or beer, but there was no decrease in BP after 4 weeks of dealcoholized red wine. Again in this study in women, higher volume red wine increased BP relative to both lower volume red wine and dealcoholized red wine. BP levels after consuming low volume red wine or dealcoholized red wine were identical offering no support for the concept that red wine polyphenolics lower BP. These consistent results suggest that any differences in prevalence and incidence of alcohol-related hypertension in relation to alcoholic beverage preference are likely because of unmeasured confounders. For example, wine drinkers make different dietary choices compared with beer or spirits drinkers; higher wine intake associates with a higher intake of healthy food items.

In conclusion, this intervention study confirms large-scale cross-sectional and prospective epidemiological studies that show regular moderate-to-heavy intake of alcohol raises BP in women. Our results provide no support for the concept that regular low-level alcohol intake can lower BP, suggesting that the J-shaped relationship between alcohol and BP in several studies is more likely because of the presence of unmeasured confounders.

Perspectives

This is the first randomized controlled trial of the effects of alcohol intake on 24-hour ambulatory BP in premenopausal women. We show that consumption of 2 to 3 standard drinks/d (146–218 g alcohol/wk) increases BP by an amount similar to intervention studies in men. Although small, the 2 mmHg increase in BP at a population level would increase mortality from stroke by 10% and from coronary artery disease by 7%. The study has found no effect of lower level alcohol intake (42–73 g alcohol/wk) to lower BP. This suggests that the J-shaped relationship between alcohol and BP in several studies is more likely because of unmeasured confounders. It further indicates that the consistent observation of reduced total and cardiovascular mortality with low-level alcohol intake in women is unlikely related to a reduction in BP.

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Disclosures

None.
References


What Is New?

- This study demonstrates that moderate regular alcohol consumption as red wine raises blood pressure (BP) in premenopausal women. Awake systolic and diastolic BP were 2.3/1.3 mm Hg higher in women consuming 2 to 3 standard drinks/d as red wine for 4 weeks when compared with a similar period when only dealcoholized red wine was consumed.

What Is Relevant?

- The results indicate that in premenopausal women alcohol raises BP by a magnitude similar to that reported in men. There was no effect of low-level alcohol intake (≈0.5–1 standard drinks/d) to lower BP suggesting that the J-shaped relationship observed between alcohol and BP in several previous studies may be because of unmeasured confounders.

Summary

This intervention study supports results from large-scale prospective epidemiological studies in confirming a direct effect of regular alcohol consumption to raise BP in women. It provides no evidence that regular low-level alcohol intake lowers BP in women. Limiting excessive alcohol consumption is, therefore, important in the prevention and treatment of hypertension in female and male drinkers alike.
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ONLINE DATA SUPPLEMENT

A RANDOMIZED CONTROLLED INTERVENTION OF THE EFFECTS OF ALCOHOL ON BLOOD PRESSURE IN PRE-MENOPAUSAL WOMEN

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Short Title: Alcohol and blood pressure in women
### Table S1 – Baseline characteristics (N=24)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>39.3 ± 7.3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.6 ± 3.3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66.4 ± 9.8</td>
</tr>
<tr>
<td>24hr Systolic BP (mm Hg)</td>
<td>110.2 ± 8.9</td>
</tr>
<tr>
<td>24hr Diastolic BP (mm Hg)</td>
<td>68.9 ± 5.7</td>
</tr>
<tr>
<td>24hr Heart rate (bpm)</td>
<td>74.6 ± 7.0</td>
</tr>
<tr>
<td>Smoking status</td>
<td>16 ex-smokers / 8 non-smokers</td>
</tr>
<tr>
<td>Alcohol intake (g/wk)</td>
<td>202±94</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>4.30 ± 0.48</td>
</tr>
<tr>
<td>Insulin (mU/L)</td>
<td>5.72 ± 2.68</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>4.69 ± 0.77</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L)</td>
<td>2.31 ± 0.71</td>
</tr>
<tr>
<td>HDL–cholesterol (mmol/L)</td>
<td>1.99 ± 0.41</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>0.84 ± 0.32</td>
</tr>
<tr>
<td>γ-GT</td>
<td>15.4 ± 8.6</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>2.8 ± 0.5</td>
</tr>
<tr>
<td>24hr urinary sodium (mmol/d)</td>
<td>136 ± 39</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± standard deviation

BMI, body mass index; γ-GT, gamma-glutamyl transpeptidase; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
Figure S1

Study design

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>0</td>
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<tr>
<td>4</td>
<td>↑</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>12</td>
<td>↑</td>
<td>↑</td>
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</tr>
</tbody>
</table>

24hr Ambulatory BP  
Fasting blood sample

Block randomization to commence either:

1. **Alcohol as higher volume red wine**
   - (a) Lower level drinkers: 200 ml/day
   - (b) Higher level drinkers: 300 ml/day
   or
2. **Alcohol as lower volume red wine**
   - (a) Lower level drinkers: 100 ml on each of 4 days/wk
   - (b) Higher level drinkers: 100 ml/day
   or
3. **Identical de-alcoholised red wine**
   - (a) Lower level drinkers: 200 ml/day
   - (b) Higher level drinkers: 300 ml/day