Alcohol Consumption and Risk of Stroke in Women

Monik Jimenez, ScD; Stephanie E. Chiuve, ScD; Robert J. Glynn, PhD, ScD; Meir J. Stampfer, MD, DrPH; Carlos A. Camargo, Jr, MD, DrPH; Walter C. Willett, MD, DrPH; JoAnn E. Manson, MD, DrPH; Kathryn M. Rexrode, MD, MPH

Background and Purpose—Light-to-moderate alcohol consumption has been consistently associated with lower risk of heart disease, but data for stroke are less certain. A lower risk of stroke with light-to-moderate alcohol intake has been suggested, but the dose response among women remains uncertain and the data in this subgroup have been sparse.

Methods—A total of 83,578 female participants of the Nurses’ Health Study who were free of diagnosed cardiovascular disease and cancer at baseline were followed-up from 1980 to 2006. Data on self-reported alcohol consumption were assessed at baseline and updated approximately every 4 years, whereas stroke and potential confounder data were updated at baseline and biennially. Strokes were classified according to the National Survey of Stroke criteria.

Results—We observed 2171 incident strokes over 1,695,324 person-years. In multivariable adjusted analyses, compared to abstainers, the relative risks of stroke were 0.83 (95% CI, 0.75–0.92) for <5 g/d, 0.79 (95% CI, 0.70–0.90) for 5 to 14.9 g/d, 0.87 (0.72–1.05) for 15 to 29.9 g/d, and 1.06 (95% CI, 0.86–1.30) for 30 to 45 g/d. Results were similar for ischemic and hemorrhagic stroke.

Conclusions—Light-to-moderate alcohol consumption was associated with a lower risk of total stroke. In this population of women with modest alcohol consumption, an elevated risk of total stroke related to alcohol was not observed. (Stroke. 2012;43:00-00.)

Key Words: alcohol ■ ischemic stroke ■ risk factors ■ stroke ■ subarachnoid hemorrhage

The association between alcohol consumption and risk of stroke remains debated with regard to associations by dose, sex, and stroke type. Some studies have suggested a lower risk of stroke among those with light-to-moderate alcohol intake, and a possibly greater risk at higher levels, but the inflection point is uncertain and the shape of the dose response may vary by gender. A meta-analysis by Reynolds et al. observed a greater risk reduction for stroke associated with low-to-moderate alcohol consumption among women than men; however, prospective cohort data were limited, especially at higher levels of intake. Further, the association may differ by stroke type and the shape of the dose response may vary by gender within types. For example, a linear association between alcohol consumption and hemorrhagic stroke has been suggested but may characterize the association only among men; therefore, more data are needed.

Furthermore, consumption patterns vary substantially between genders; only 42% of women reported drinking ≥12 drinks in the past year compared to 60% of men. Most studies have utilized only baseline assessments of alcohol consumption, which fail to account for changes in alcohol consumption over time. Moreover, studies to date have not evaluated potential effect modification by key risk factors such as age or hormone therapy use in women. Finally, few studies have adequately adjusted for confounding by lifestyle or socioeconomic factors and have been limited by few events.

In our previous work from this cohort, Chiuve et al. observed a significantly lower risk of stroke for alcohol consumption <15 g/d compared to abstainers; however, this was not the main focus of the analysis. Therefore, we have analyzed the association between alcohol intake and risk of total, ischemic, and hemorrhagic stroke in more detail with special consideration of factors specific to alcohol consumption, such as a detailed analysis of former drinkers and lifetime abstainers using updated information on alcohol intake over time. Importantly, we evaluated whether these associations varied by age, hormone use, aspirin use, hypertension, smoking status, and history of atrial fibrillation.

Materials and Methods

Study Population
The Nurses’ Health Study enrolled 121,700 female registered nurses living in 11 U.S. states, aged 30 to 55 years, who completed a mailed

Received September 19, 2011; accepted December 22, 2011.

Ralph L. Sacco, MD, was the Guest Editor for this paper.

From the Division of Preventive Medicine (M.J., S.E.C., R.J.G., J.E.M., K.M.R.), Brigham and Women’s Hospital, Boston, MA; Department of Nutrition (S.E.C., M.J.S., W.C.W.), Harvard School of Public Health, Boston, MA; Channing Laboratory (M.J.S., C.A.C., W.C.W., J.E.M.), Department of Medicine, Brigham and Women’s Hospital, Boston, MA; Department of Epidemiology (M.J.S., C.A.C., W.C.W., J.E.M.), Harvard School of Public Health, Boston, MA; and Department of Biostatistics (R.J.G.), Harvard School of Public Health, Boston, MA.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.orglookup/suppl/doi:10.1161/STROKEAHA.111.639435/-/DC1.

Correspondence to Kathryn M. Rexrode, MD, MPH, 900 Commonwealth Avenue, 3rd Floor, Boston, MA 02215. E-mail krrexrode@partners.org

© 2012 American Heart Association, Inc.
questionnaire in 1976. Follow-up questionnaires are mailed biennially, with a semiquantitative food frequency questionnaire mailed approximately every 4 years since 1980. Detailed descriptions of the Nurses’ Health Study have been previously published. Women were excluded from the analysis if they were abstainers at baseline in 1980 and reported “greatly decreasing” their alcohol intake in the previous 10 years (potentially “sick quitters,” n = 3,712), if alcohol data at baseline were missing, if they consumed >45 g/d (>1% of population; 31 events), if they reported a history of stroke (n = 268), cancer (except nonmelanoma skin cancer; n = 3,394), cardiovascular disease (myocardial infarction, coronary artery bypass graft surgery, and angio/plast; n = 597), or if they had missing date of birth. The final sample consisted of 83,578 women.

Alcohol and Diet Assessment
In 1980, 1984, 1986, and every 4 years thereafter, participants were asked to complete a food frequency questionnaire on their intake of specific foods and beverages, each with specified portion size, during the previous 12 months. Separate questions asked about the consumption of wine (4 oz [120 mL] until 2004, 5 oz [148 mL] thereafter), beer (12 oz [360 mL]), and spirits (1.5 oz [44 mL]). Beer was assumed to contain 13 g (regular, 13 g; light, 11 g), wine 11 g (4 oz, 11 g; 5 oz, 13.6 g), and spirits 14 g of alcohol per serving. Total alcohol was calculated as the sum of all 3 beverage types and categorized (0, >0–4.9, 5–14.9, 15–29.9, 30–45 g/d) to maintain consistency with the literature. Former drinkers were defined using questions on patterns of consumption collected in 1988, 1996, 2000, and 2004 (online-only Supplemental Methods, http://stroke.ahajournals.org). Alcohol consumption obtained on 2 food frequency questionnaires were reproduced against 4 1-week diet records taken 3 months apart with correlation coefficients ranging from 0.86 to 0.90. Furthermore, reported alcohol was significantly correlated with serum high-density lipoprotein levels (r = 0.40; P < 0.001).

Cerebrovascular Disease Assessment
These analyses included all nonfatal and fatal strokes diagnosed after the return of the 1980 questionnaire but before June 2006. Women (or next-of-kin for decedents) reporting stroke on follow-up questionnaires were asked for permission to review medical records, which were reviewed by a physician blinded to exposure status. We excluded cerebrovascular pathology attributable to infection, trauma, malignancy, and “silent” strokes discovered only by radiological imaging. Stroke was classified according the National Survey of Stroke criteria requiring evidence of a neurological deficit with lesion that increased in size or symptom severity (ischemic, hemorrhagic, and strokes of probable/unknown subtype), hemorrhagic stroke (subarachnoid hemorrhage, intraparenchymal hemorrhage), or stroke of probable/unknown subtype when a stroke was documented but the subtype could not be ascertained because of unavailable medical records. They classified stroke as probable if the supporting information was provided, but medical records were not available or only a death certificate was available. Seventy-six percent of total strokes were confirmed by medical records or death certificate documentation (medical records: n = 1,556; death certificate: n = 106), whereas 27% were probable of unspecified subtype because of unavailable medical record documentation (n = 396). The primary end points for this study were total (ischemic, hemorrhagic, and strokes of probable/unknown subtype), ischemic, and hemorrhagic stroke. Deaths were detected through information provided by the next of kin, postal authorities, or by systematic searches of the National Death Index. Classification of fatal stroke was confirmed by review of hospital records or autopsy. Analyses were repeated excluding probable events and results were similar; therefore, the analyses presented include both confirmed and probable events.

Statistical Analysis
Descriptive analyses for baseline characteristics were conducted for the full cohort and separately by categories of alcohol intake. Age and multivariable adjusted time-varying Cox models were used to estimate hazard ratios and corresponding 95% CI for the association between alcohol consumption and risk of stroke using age (months) as the underlying time scale stratified by calendar year (questionnaire cycle). Participants contributed follow-up from the date of return of the 1980 questionnaire until the earliest of the following: death, stroke, or June 2006.

Data on all covariates were collected on each biennial questionnaire, with the exception of height (collected in 1976), atrial fibrillation (collected beginning in 2000), education (collected in 1992), marital status (1992, 1996, and 2000), and dietary variables (collected every 4 years). All models adjusted for smoking. Multivariable models additionally adjusted for physical activity, body mass index (kg/m²), family history of heart disease, history of heart disease, diabetes, and hypertension, bilateral oophorectomy, postmenopausal status, hormone therapy, high cholesterol, multivitamin intake, aspirin, composite 6-nutrient diet score, highest level of education, husband’s highest level of education, and marital status (online-only Supplemental Methods). To address missing information, data were carried forward ≤1 questionnaire cycle, and the missing indicator method was used to model missing values in categorical variables.

In primary analyses, we modeled alcohol consumption utilizing the most recent alcohol intake, based on acute effects on blood pressure, platelets, and thrombotic factors. In secondary analyses, we modeled the cumulative average of alcohol consumption over follow-up that assumes long-term exposure to alcohol as the biological mechanism. A priori we proposed to evaluate effect modification by selected risk factors, age, hypertension status, aspirin use, smoking status, hormone therapy, and atrial fibrillation. History of atrial fibrillation was ascertained beginning in 2000; hence, this analysis utilized a subgroup (n = 51,846). Effect modification was assessed by a likelihood ratio test comparing a model including interaction terms to a model with main effects only.

We examined a nonlinear relation between alcohol consumption and incident total stroke nonparametrically with restricted cubic splines based on 3 knots of alcohol consumption located at the 5th, 50th, and 95th percentiles. Tests for nonlinearity used the likelihood ratio test comparing the model with only the linear term to the model with the linear and the cubic spline terms. In sensitivity analyses, we stopped updating alcohol exposure on self-report of hypertension, diabetes, myocardial infarction, coronary artery bypass graft surgery, angio/plast, or cancer to assess potential bias attributable to change in alcohol consumption as a consequence of diagnosis. We conducted a separate analysis categorizing nondrinkers separately as former drinkers or abstainers. Additionally, we examined an alternate upper category of alcohol consumption (>45 g/d; n = 84,611; total stroke = 2,202). We also evaluated whether the association differed according to alcohol type. Residual confounding by smoking status was examined by subgroup analysis among never smokers. All P values are 2-sided. Analyses were conducted with SAS for UNIX statistical software (version 9.1.3; SAS Institute). This study was approved by the Institutional Review Board of Brigham and Women’s Hospital and all procedures followed were in accordance with institutional guidelines. Participants provided informed consent to participate.

Results
The baseline characteristics of the study population by categories of alcohol consumption are shown in Table 1. The mean age at baseline was 46 years. Approximately 30% of women reported no alcohol consumption, 35% reported very low levels of intake (≤ 1/2 glass/d), and 4% reported 30 to 45 g/d (~2–3 glasses/d). Overall, heavier alcohol consumption was associated with a higher prevalence of current smoking, history of hypertension, increased physical activity, and lower body mass index compared to abstainers.

Over 26 years of follow-up, we documented 2,171 total stroke events, 1,206 of which were ischemic, 363 were...
hemorrhagic, and 602 were of probable/unknown subtype. In multivariable analyses, low (0–4.9 g/d) and moderate (5–14.9 g/d) consumptions were associated with lower risk of total stroke compared to abstainers (Table 2), whereas women who consumed 30 to 45 g/d did not have a greater risk of total stroke. The Figure shows the nonlinear J-shape association between alcohol consumption and risk of incident total stroke (P=0.001 for deviation from linearity). Greater risk of stroke was observed for alcohol intake $>$36 g/d; however, the confidence limits were exception-
ally wide because of few events in the higher range of intake. In sensitivity analyses, former drinkers did not exhibit an elevated risk compared to lifetime abstainers (data not shown).

In multivariable analyses, the associations between alcohol consumption and ischemic stroke were similar, but not statistically significant. Intake of 30 to 45 g/d was suggestive of a nonsignificant increased risk of ischemic stroke. There was no association between alcohol consumption (30–45 g/d) and risk of hemorrhagic stroke when compared to abstainers.

Stratified analyses by key risk factors were performed (Table 3). There was no evidence to suggest that the association varied significantly by age, hypertension, aspirin use, hormone therapy, or smoking. However, there was a suggestion that the association varied by history of atrial fibrillation, with a significantly lower risk of total stroke among moderate drinkers (0–29.9 g/d) without a history of atrial fibrillation (P for interaction=0.03).

In sensitivity analyses, we also modeled alcohol intake using a cumulative method and obtained similar results as our main analysis using recent intake. We additionally examined an alternate upper category of $>$45 g/d, which utilized more observations and results were similar to those of our main analysis despite limited power ($>$45 g/d; hazard ratio, 1.03; 95% CI, 0.71–1.48). We considered a multivariable model without adjustment for hypertension, because it may be part of the causal pathway, but results were materially unchanged (data not shown). Analyses by alcohol type provided similar results (results not shown). To assess a potential bias attributable to changes in alcohol consumption as a consequence of chronic disease diagnosis, we stopped updating alcohol exposure on self-reports of chronic disease and observed similar results (data not shown). Last, there was no evidence of residual confounding by smoking, shown by similar results among never smokers (Table 3).

**Discussion**

In this population of nearly 85,000 women who were free of reported cardiovascular disease at baseline, we observed an

---

**Table 1. Baseline Characteristics of Population by Categories of Alcohol Consumption in 1980**

<table>
<thead>
<tr>
<th>Alcohol Intake Categories, g/d (Median)</th>
<th>None (0)</th>
<th>$&gt;$0–4.9 (1.8)</th>
<th>5.0–14.9 (10.2)</th>
<th>15.0–29.9 (19.5)</th>
<th>30–45 (35.8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N, %</td>
<td>25,134 (30%)</td>
<td>29,420 (35%)</td>
<td>19,544 (23%)</td>
<td>6093 (7%)</td>
<td>3387 (4%)</td>
</tr>
<tr>
<td>Age</td>
<td>46.1±7.2</td>
<td>46.0±7.3</td>
<td>46.1±7.1</td>
<td>46.3±6.9</td>
<td>46.4±6.9</td>
</tr>
<tr>
<td>White, %</td>
<td>97</td>
<td>98</td>
<td>98</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>Alcohol consumed (g/d)</td>
<td>0</td>
<td>1.9±1.2</td>
<td>9.7±3.0</td>
<td>20.9±4.7</td>
<td>36.1±3.4</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.3±5.1</td>
<td>24.5±4.4</td>
<td>23.5±3.7</td>
<td>23.2±3.5</td>
<td>23.4±3.6</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never, %</td>
<td>59</td>
<td>45</td>
<td>34</td>
<td>27</td>
<td>19</td>
</tr>
<tr>
<td>Past, %</td>
<td>19</td>
<td>28</td>
<td>34</td>
<td>38</td>
<td>28</td>
</tr>
<tr>
<td>Current, %</td>
<td>22</td>
<td>27</td>
<td>33</td>
<td>35</td>
<td>53</td>
</tr>
<tr>
<td>Hormone therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal, %</td>
<td>61</td>
<td>62</td>
<td>62</td>
<td>62</td>
<td>61</td>
</tr>
<tr>
<td>Never users, %</td>
<td>26</td>
<td>25</td>
<td>24</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>Past users, %</td>
<td>11</td>
<td>11</td>
<td>10</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Current users, %</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Multivitamin use, %</td>
<td>32</td>
<td>34</td>
<td>35</td>
<td>37</td>
<td>35</td>
</tr>
<tr>
<td>Physical activity, % (hr/wk)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\geq$6</td>
<td>18</td>
<td>22</td>
<td>26</td>
<td>28</td>
<td>23</td>
</tr>
<tr>
<td>3.5–6</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>1.0–3.5</td>
<td>32</td>
<td>31</td>
<td>28</td>
<td>26</td>
<td>30</td>
</tr>
<tr>
<td>$&lt;$1.0</td>
<td>37</td>
<td>34</td>
<td>33</td>
<td>33</td>
<td>36</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>1</td>
<td>0.5</td>
<td>0.3</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>17</td>
<td>15</td>
<td>15</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>High cholesterol, %</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Family history of myocardial infarction, %</td>
<td>20</td>
<td>21</td>
<td>21</td>
<td>20</td>
<td>21</td>
</tr>
</tbody>
</table>

Values are means±SD or percentages and all values, except age, are standardized to the age distribution of the study population.
inverse association between low-to-moderate alcohol consumption and risk of total stroke. We observed a lower risk at low-to-moderate intakes and a suggestion toward greater risk of ischemic stroke at intakes of 30 to 45 g/d. Low-to-moderate alcohol consumption was not associated with a greater risk of hemorrhagic stroke in this population. We had limited power to evaluate heavy drinking; only 1% of women reported consuming >45 g/d.

Table 2. Multivariable* Association Between Alcohol and Incidence of Total, Ischemic, and Hemorrhagic Stroke

<table>
<thead>
<tr>
<th>N=83,578</th>
<th>Alcohol Intake Categories, g/day</th>
<th>P, Deviation From Linearity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
<td>&gt;0–4.9</td>
</tr>
<tr>
<td>Total stroke Events</td>
<td>2171</td>
<td>1045</td>
</tr>
<tr>
<td>Smoking-adjusted HR (95%CI)</td>
<td>1.00</td>
<td>0.74 (0.67–0.82)</td>
</tr>
<tr>
<td>Multivariable model HR (95%CI)</td>
<td>1.00</td>
<td>0.83 (0.75–0.92)</td>
</tr>
<tr>
<td>Ischemic stroke Events</td>
<td>1206</td>
<td>566</td>
</tr>
<tr>
<td>Smoking-adjusted HR (95%CI)</td>
<td>1.00</td>
<td>0.78 (0.68–0.90)</td>
</tr>
<tr>
<td>Multivariable model HR (95%CI)</td>
<td>1.00</td>
<td>0.88 (0.76–1.02)</td>
</tr>
<tr>
<td>Hemorrhagic stroke Events</td>
<td>363</td>
<td>156</td>
</tr>
<tr>
<td>Smoking-adjusted HR (95%CI)</td>
<td>1.00</td>
<td>0.76 (0.59–0.98)</td>
</tr>
<tr>
<td>Multivariable model HR (95%CI)</td>
<td>1.00</td>
<td>0.82 (0.63–1.06)</td>
</tr>
</tbody>
</table>

Multivariable model covariates: smoking, physical activity, body mass index kg/m², history of heart disease, family history of heart disease, history of diabetes, bilateral oophorectomy, postmenopausal status, use of hormone therapy, high cholesterol, multivitamin intake, aspirin intake, 6-nutrient diet score, highest level of education achieved, husband’s level of education, and marital status.

CI indicates confidence interval; HR, hazard ratio.

*All models adjusted for age (mo).
Table 3. Multivariable Association Between Alcohol and Total Stroke Stratified by Key Risk Factors

<table>
<thead>
<tr>
<th>Alcohol Intake Categories, g/day</th>
<th>None</th>
<th>&lt;0–4.9</th>
<th>5.0–14.9</th>
<th>15.0–29.9</th>
<th>30–45</th>
<th>( P ) for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Stroke</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Younger than 60</td>
<td>822</td>
<td>399</td>
<td>239</td>
<td>94</td>
<td>75</td>
<td>0.75</td>
</tr>
<tr>
<td>Age 60 or older</td>
<td>223</td>
<td>153</td>
<td>102</td>
<td>37</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>613</td>
<td>278</td>
<td>163</td>
<td>55</td>
<td>58</td>
<td>0.57</td>
</tr>
<tr>
<td>No</td>
<td>432</td>
<td>274</td>
<td>178</td>
<td>76</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td><strong>Aspirin use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonuser</td>
<td>484</td>
<td>243</td>
<td>145</td>
<td>59</td>
<td>47</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>1–5/wk</td>
<td>133</td>
<td>89</td>
<td>55</td>
<td>20</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>≥6/wk</td>
<td>428</td>
<td>220</td>
<td>141</td>
<td>52</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td><strong>Hormone therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>360</td>
<td>161</td>
<td>115</td>
<td>36</td>
<td>25</td>
<td>0.19</td>
</tr>
<tr>
<td>Past</td>
<td>337</td>
<td>154</td>
<td>98</td>
<td>47</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>300</td>
<td>192</td>
<td>104</td>
<td>39</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>493</td>
<td>180</td>
<td>88</td>
<td>28</td>
<td>16</td>
<td>0.56</td>
</tr>
<tr>
<td>Former</td>
<td>382</td>
<td>241</td>
<td>153</td>
<td>66</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>170</td>
<td>131</td>
<td>100</td>
<td>37</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td><strong>Atrial fibrillation</strong>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>63</td>
<td>19</td>
<td>16</td>
<td>14</td>
<td>7</td>
<td>0.03</td>
</tr>
</tbody>
</table>

(Continued)
Our results are generally consistent with previous studies. Reynolds et al. reported 20% to 30% lower risk of total stroke for men and women at low levels of intake and a nearly 4-fold greater risk at the highest level (≥60 g/d) compared to abstainers (P<0.001 nonlinear trend), which was based on 35 studies; however, only 16 were among women. In the Framingham Heart Study, one of the few studies with multiple assessments and lengthy follow-up, there was no clear association between alcohol consumption and risk of ischemic stroke among women. Overall, the data indicate a modestly lower risk of ischemic stroke for low-to-moderate alcohol consumption with a potentially greater risk at levels beyond the range observed in our study.

Data for hemorrhagic stroke have been inconsistent, with some suggesting a linearly increasing association1 and others suggesting increased risk only at higher levels of intake. Patra et al. reported a J-shape association between alcohol consumption and hemorrhagic stroke among women, with an inverse association for ≤36 g/d, in contrast to a linear association among men; however, the data among women were based on a mere 8 studies. Our results are similar but underpowered at high levels of consumption.

We conducted several a priori stratified analyses and observed significant effect modification by atrial fibrillation. Moderate alcohol consumption was only associated with a lower risk of total stroke compared to abstention among women without a history of atrial fibrillation. Alcohol may increase risk of atrial fibrillation, leading to greater risk of atrial clot formation and embolic stroke; however, these analyses were likely underpowered. Because alcohol has been shown to increase serum estrogen levels among women using hormone therapy, we hypothesized that alcohol might amplify the risk of stroke observed with hormone therapy; however, the interaction was not statistically significant. Chang findings associated with evaluation of multiple subgroups may also explain apparent heterogeneity.

Alcohol may influence risk of stroke through several mechanisms dependent on level of consumption. Alcohol consumption may be antithrombotic and atherogenic, leading to increased high-density lipoprotein, decreased platelet aggregation, clot formation, and increased fibrinolysis. This may simultaneously lower risk of ischemic while increasing risk of hemorrhagic stroke. Higher levels of alcohol consumption may increase risk of ischemic and hemorrhagic stroke through both acute and chronic effects on blood pressure. Alcohol may influence risk of stroke through acute (eg, atrial fibrillation and blood pressure) and chronic processes (eg, atherosclerosis), shown by the similar results obtained in sensitivity analyses examining recent and cumulative intakes. Notably, the inverse association between alcohol and coronary heart disease is substantially stronger than for stroke, exhibiting a linear dose–response curve. Unidentified risk factors or differences in the strength of the associations for alcohol with key risk factors for stroke and coronary heart disease (eg, hypertension) may explain these differences.

Alcohol consumption was measured using self-reported food frequency questionnaires with high reproducibility in this population and validity against plasma high-density lipoprotein. We cannot rule out bias because of underreporting alcohol, potentially leading to spurious associations at lower levels of consumption. Adjustment for various demographic, lifestyle, and dietary factors had a marginal influence on the association, minimizing potential unmeasured confounding by lifestyle factors.

We had limited power to assess heavy alcohol consumption and drinking patterns (eg, binge drinking) because of variable collection and the range of available data. Although the gender and demographic composition of the Nurses’ Health Study potentially limit generalizability to men or ethnically diverse populations, similar results have been reported across diverse populations, with the exception of particular Asian populations (eg, Japanese).

Important strengths include the large sample size, longitudinal design with 26 years of follow-up, and updated information on alcohol and confounders. Furthermore, we conducted detailed analyses to address changes in alcohol consumption over time, because of behavior, chronic disease, or dependency.

### Conclusions

In this population of women, modest alcohol consumption was not associated with an elevated stroke risk within the range of alcohol consumption observed in this cohort. Low-to-moderate alcohol consumption was associated with a modestly lower risk of total stroke. Hence, our data are consistent with the current American Heart Association guidelines for women, suggesting a modest inverse association between alcohol consumption of ≤1 drink per day with risk of total, ischemic, and hemorrhagic stroke.
Sources of Funding
HL088521-S1 and HL34594 from the National Heart, Lung, and Blood Institute of the National Institutes of Health and CA87969 from the National Cancer Institute.

Disclosures
None.

References
Alcohol Consumption and Risk of Stroke in Women
Monik Jimenez, Stephanie E. Chiuve, Robert J. Glynn, Meir J. Stampfer, Carlos A. Camargo, Jr, Walter C. Willett, JoAnn E. Manson and Kathryn M. Rexrode

Stroke. published online March 8, 2012;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628
The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2012/03/07/STROKEAHA.111.639435
Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2012/03/08/STROKEAHA.111.639435.DC1
http://stroke.ahajournals.org/content/suppl/2013/10/08/STROKEAHA.111.639435.DC2

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/
SUPPLEMENTAL MATERIAL

Alcohol pattern questions

In 1980, participants were asked whether the consumption of each item had greatly increased or decreased over the previous 10 years. Further, in 1988, 1996, 2000 and 2004 questions on pattern of alcohol consumption were collected, including frequency of weekly alcohol consumption, greatest number of drinks in a day, and alcohol consumption over the life span, which were used to define former drinkers.

Covariate Ascertainment

Marital status was considered to remain constant between 1980 and assessment in 1992; 81% of women reported being married in 1992. Smoking was adjusted for in all models using the following classification, never, past, 1-14 cig/day, 14-24 cig/d, 25+ cig/day and current/unknown quantity. Multivariable models used the following classification of variables: physical activity (>6, 5.9-3.5, 3.49-1.0, <1.0 hrs/day), body mass index (BMI; <18.5, 18.5-24.9,25-29.9, >30 kg/m²), history of heart disease (yes/no), family history of heart disease (yes/no), history of diabetes (yes/no), history of hypertension (yes/no), bilateral oophorectomy (yes/no), postmenopausal status (premenopausal, menopausal, post-menopausal), hormone therapy (never, past, current user), high cholesterol (yes/no), multivitamin intake (yes/no), aspirin (<1 tablet/wk, 1-5 tablets/wk, >6 tablets/week), composite 6 nutrient diet score¹ based on a diet low in trans fat and glycemic load, high in cereal fiber, marine n-3 fatty acids, folate and high ratio of polyunsaturated to saturated fat (quintiles), highest level of education (master or doctorate/registered nurse or bachelor degree), husband’s highest level of education (<high school graduate/college graduate or graduate school), and marital status. Physical activity, diet, hormonal status and
chronic disease outcomes (hypertension, diabetes and heart disease) have been previously validated in this or similar populations.\textsuperscript{2-5}

\textbf{References:}

Alcohol Consumption and Risk of Stroke in Women

Monik Jimenez, ScD; Stephanie E. Chiuve, ScD; Robert J. Glynn, PhD, ScD; Meir J. Stampfer, MD, DrPH; Carlos A. Camargo, Jr, MD, DrPH; Walter C. Willett, MD, DrPH;JoAnn E. Manson, MD, DrPH; Kathryn M. Rexrode, MD, MPH

(Stroke. 2012;43:939-945.)

Key Words: alcohol  ■ ischemic stroke  ■ risk factors  ■ stroke  ■ subarachnoid hemorrhage

Table 2. Multivariable* Association Between Alcohol and Incidence of Total, Ischemic, and Hemorrhagic Stroke

<table>
<thead>
<tr>
<th>Alcohol Intake Categories, g/day</th>
<th>None</th>
<th>&gt;0–4.9</th>
<th>5.0–14.9</th>
<th>15.0–29.9</th>
<th>30–45</th>
<th>P, Deviation From Linearity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total stroke</td>
<td>2171</td>
<td>1045</td>
<td>552</td>
<td>341</td>
<td>131</td>
<td>102</td>
</tr>
<tr>
<td>Events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking-adjusted HR (95% CI)</td>
<td>1.00</td>
<td>0.74 (0.67–0.82)</td>
<td>0.66 (0.58–0.75)</td>
<td>0.71 (0.59–0.86)</td>
<td>0.94 (0.76–1.16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multivariable model HR (95% CI)</td>
<td>1.00</td>
<td>0.83 (0.75–0.92)</td>
<td>0.79 (0.70–0.90)</td>
<td>0.87 (0.72–1.05)</td>
<td>1.06 (0.86–1.30)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1206</td>
<td>566</td>
<td>318</td>
<td>196</td>
<td>65</td>
<td>61</td>
</tr>
<tr>
<td>Events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking-adjusted HR (95% CI)</td>
<td>1.00</td>
<td>0.78 (0.68–0.89)</td>
<td>0.71 (0.60–0.84)</td>
<td>0.67 (0.52–0.87)</td>
<td>1.06 (0.81–1.39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multivariable model HR (95% CI)</td>
<td>1.00</td>
<td>0.88 (0.76–1.02)</td>
<td>0.86 (0.72–1.02)</td>
<td>0.82 (0.63–1.07)</td>
<td>1.17 (0.89–1.54)</td>
<td>0.002</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>363</td>
<td>156</td>
<td>97</td>
<td>65</td>
<td>27</td>
<td>18</td>
</tr>
<tr>
<td>Events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking-adjusted HR (95% CI)</td>
<td>1.00</td>
<td>0.76 (0.59–0.98)</td>
<td>0.71 (0.53–0.96)</td>
<td>0.84 (0.55–1.27)</td>
<td>0.91 (0.55–1.49)</td>
<td>0.89</td>
</tr>
<tr>
<td>Multivariable model HR (95% CI)</td>
<td>1.00</td>
<td>0.82 (0.63–1.06)</td>
<td>0.76 (0.56–1.03)</td>
<td>0.88 (0.58–1.35)</td>
<td>0.97 (0.58–1.60)</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Multivariable model covariates: smoking, physical activity, body mass index kg/m², history of heart disease, family history of heart disease, history of diabetes, bilateral oophorectomy, postmenopausal status, use of hormone therapy, high cholesterol, multivitamin intake, aspirin intake, 6-nutrient diet score, highest level of education achieved, husband’s level of education, and marital status.
CI indicates confidence interval; HR, hazard ratio.*All models adjusted for age (mo).