Alcohol Consumption at Midlife and Risk of Stroke During 43 Years of Follow-Up
Cohort and Twin Analyses

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Background and Purpose—Although alcohol–stroke association is well known, the age-varying effect of alcohol drinking at midlife on subsequent stroke risk across older adulthood has not been examined. The effect of genetic/early-life factors is also unknown. We used cohort and twin analyses of data with 43 years of follow-up for stroke incidence to help address these gaps.

Methods—All 11644 members of the population-based Swedish Twin Registry born 1886 to 1925 with alcohol data aged ≤60 years were included. The interaction of midlife alcohol consumption by age at stroke was evaluated in Cox-regression and analyses of monozygotic twins were used. Covariates were baseline age, sex, cardiovascular diseases, diabetes mellitus, stress reactivity, depression, body mass index, smoking, and exercise.

Results—Altogether 29% participants developed stroke. Compared with very-light drinkers (<0.5 drink/d), heavy drinkers (>2 drinks/d) had greater risk of stroke (hazard ratio, 1.34; P=0.02) and the effect for nondrinkers approached significance (hazard ratio, 1.11; P=0.08). Age increased stroke risk for nondrinkers (P=0.012) and decreased it for heavy drinkers (P=0.040). Midlife heavy drinkers were at high risk from baseline until the age of 75 years when hypertension and diabetes mellitus grew to being the more relevant risk factors. In analyses of monozygotic twin-pairs, heavy drinking shortened time to stroke by 5 years (P=0.04).

Conclusions—Stroke-risk associated with heavy drinking (>2 drinks/d) in midlife seems to predominate over well-known risk factors, hypertension and diabetes, until the age of 75 years and may shorten time to stroke by 5 years above and beyond covariates and genetic/early-life factors. Alcohol consumption should be considered an age-varying risk factor for stroke. (Stroke. 2015;46:627-633. DOI: 10.1161/STROKEAHA.114.006724.)

Key Words: alcohols □ risk factors □ stroke □ twins

A lcohol has emerged as a potentially important factor with a J- or U-shaped association to stroke risk.1 Although the association between alcohol and cardiovascular diseases was a point of interest ≥3 decades ago, there are still considerable gaps in knowledge in this area.

Statistical methods commonly used in previous studies, Cox-regression or logistic regression, model overall effects as opposed to time-varying effects, which do not allow modeling of disease risk associated with alcohol consumption by age. A contribution by genetic and early-life factors has been found for alcohol consumption,2 as well as for stroke,3,4 but has not been assessed for the alcohol–stroke association. Furthermore, data on monozygotic twins concordant for stroke allow highly controlled examination of time to stroke as a function of alcohol consumption.

Data from a population-based cohort of middle-aged Swedish twins and 43 years of follow-up give us the opportunity to examine effects of genetic/early-life factors and age-varying effects to stroke risk.5–10 Specifically, we tested the hypothesis that heavy drinkers and nondrinkers would have a greater risk of stroke compared to very-light drinkers. We chose very-light drinkers (as opposed to nondrinkers) as the reference category to avoid potential bias caused by ex-drinkers who had stopped drinking alcohol for health problems and may possess preexisting susceptibilities. Trying to fill a gap in knowledge on variance of the association between stroke risk and alcohol consumption, we tested explicitly whether stroke risk associated with alcohol consumption is stable over time. Finally, we add to previous research by examining the role of genetic and early-life factors in alcohol–stroke association by examining differences in time to stroke caused by alcohol consumption within monozygotic twins concordant for stroke.

Methods

The analyzed cohort, known as the old cohort of the Swedish Twin Registry, is based on records of all like-sexed twins born between 1886 and 1925, residing in Sweden, and responding to a questionnaire in 1960.
to 1961. A questionnaire specifically designed to assess alcohol drinking and smoking was sent in 1967 to all 20,902 subjects who had responded to the initial questionnaire. Subjects aged ≥60 years at baseline and valid alcohol data were analyzed. Creation of the analytic data set (n=11,644) is illustrated in Figure 1. The registry has been linked regularly to the national healthcare registries, namely the inpatient and cause of death registries, to obtain diagnostic information. For our study last diagnostic data were obtained in year 2010, offering a 43-year follow-up. Data collection is described in detail by Lichtenstein et al.11

Primary Outcome
Stroke and transient ischemic attack events were selected from the national registers according to the International Classification of Disease (ICD) codes as follows: All stroke and transient ischemic attack events: 330 to 334 (ICD-Seventh Revision), 430 to 438 (ICD-Eighth and Ninth Revision), I60 to I69, G45.3, G45.4, G45.8, G45.9 (ICD-Tenth Revision); ischemic events: 332 (ICD-7), 432 to 435, 437 to ICD-8, 433 to 435 (ICD-9), I63, I65, I66, and G45 (ICD-10); and hemorrhagic events: 330 and 331 (ICD-7), 430 and 431 (ICD-8), 430 to 432 (ICD-9), I60 to I62 (ICD-10). Only the first event was used.

Assessment of Alcohol Consumption
Data on alcohol consumption were collected using the following questions: Did you drink beer, wine, or liquor at any time during the past year (Yes/No)? And if No: Did you drink alcohol before that time (Yes/No)? Those who had answered No to both of these questions and stopped answering questions about alcohol were classified as nondrinkers.

Those who had answered Yes to one of these questions were asked additional questions to obtain more detailed information about frequency and quantity of beer, wine, and spirits consumed. To be able to compare the results with current guidelines,12 the amount of alcohol in grams per day was calculated as follows: responses were transformed to numeric values of frequency per day and quantity in liters were multiplied getting average volume of consumed alcohol per day. Volume was transformed to grams of alcohol assuming 5%, 12%, and 40% alcohol in beer, wine, and spirits, respectively, resulting in 39.5, 432, and 431 (ICD-Seventh Revision), 430 to 438 (ICD-Eighth and Ninth Revision), G45.3, G45.4, G45.8, G45.9 (ICD-Tenth Revision); ischemic events: 332 (ICD-7), 432 to 435, 437 to ICD-8, 433 to 435 (ICD-9), I63, I65, I66, and G45 (ICD-10); and hemorrhagic events: 330 and 331 (ICD-7), 430 and 431 (ICD-8), 430 to 432 (ICD-9), I60 to I62 (ICD-10). Only the first event was used. Alcohol consumption was further categorized as follows (overall and by gender): none [23% (11%/32%)], very light (>0–5 g/d; ie, <0.5 drink/d); 49% [41%/55%], light (5–12 g/d; ie, 0.5 –1 drink/d); 18% [27%/10%], moderate (>12–24 g/d; ie, 1–2 drinks/d); 9% [17%/2%], and heavy (>24 g/d; ie, >2 drinks/d); 3% [5%/0.5%]). On average, 1 drink is assumed to contain ∼12 g of alcohol. The median frequency of consumption per week was 0.5x per week for very-light drinkers, 1.5x for light drinkers, and 5x for moderate drinkers and heavy drinkers.

Covariates
The following covariates were used: baseline age, sex, preferred type of alcohol (derived as beverage with highest amount of alcohol consumed), current smoking, body mass index, exercise (hardly any, light, regular, hard training), stress reactivity, and presence/absence of the following diseases identified from the national health resisters: hypertension, diabetes mellitus type I or II, coronary heart disease, and depression. Both current smoking and current/former smoking were explored as covariates. Alternating these 2 covariates did not change study results. Stress reactivity was evaluated using the question: When you become emotionally upset or are under emotional strain, do you often experience persisting (lasting more than an hour) discomfort in the form of: Pounding headaches/Palpitations of the heart/Stomach upsets/None of above?

Statistical Methods
Statistical analysis was performed using SAS v9.3 (SAS Institute, Cary, NC). Three methods of analysis were used: cohort analysis, coxwin control analysis with monozygotic pairs discordant for stroke, and pairwise mixed-effects analysis to estimate time to stroke in monozygotic pairs discordant for stroke.

First, the entire cohort (n=11,644) was analyzed using Cox proportional hazards analysis with age as the time scale and with right censoring of event-free subjects at the time of death or the end of the study. Given the presence of twin clustering, we used a robust sandwich covariance matrix estimator.13

Furthermore, given previously discussed differences in alcohol–stroke link between men and women,14,15 and between stroke subtypes,16 hazard ratios (HRs) for men, women, ischemic stroke, and hemorrhagic stroke (only 406 events) were estimated separately in addition to overall estimates.

For Cox-regression models, proportional hazard assumptions were examined16,17 and tested statistically.18 We found that the proportionality assumption was violated in fully adjusted analyses for ≥1 alcohol category (P<0.01). Therefore, we added an alcohol category by stroke age interaction (ie, age-varying effect) to test whether effect of midlife alcohol consumption varies with increasing age in older adulthood. Previously, the strategy to include time-varying effect into Cox-regression model was found to provide meaningful results when the proportionality assumption is violated.19 Because we used age as our time scale we refer to the time-varying effect as age-varying effect in this study. In this context, it is important to note that the method requires a relatively long-term follow-up for the outcome of interest (stroke in this study) to examine properly how alcohol consumption at midlife affects subsequent risk of stroke across older adulthood (considering that the effect of alcohol consumption may not be immediate but can reveal itself later).

The possibility that death because of heart failure (cardiovascular event potentially attributed to excessive alcohol drinking) can be a competing risk event was explored: Of 528 deaths because of heart...
failure, 152 (1% of the sample) also had stroke before death. The remaining 376 (3% of the sample) could potentially have a high risk of stroke, although we cannot be certain that they would get stroke later. Therefore, considering these numbers, we do not think that heart failure was an important competing risk in this study.

For the next 2 types of analysis, the data were restricted to complete monozygotic twin-pairs, providing full control over genetic influences. Of the 4922 complete twin-pairs, 1715 (35%) were monozygotic, of whom 370 pairs were discordant for stroke (1 developed stroke, 1 did not) and 167 were concordant (both developed stroke). Conditional logistic regression (where each stratum is represented by a twin-pair) was used to examine alcohol consumption in relation to risk of stroke within the 370 discordant twin-pairs. Mixed-effects analysis with the discordant pairs was used to examine whether a certain level of alcohol consumption may prolong or hasten time to stroke.

Results
Of the 11644 analyzed participants, 3328 (29%) experienced any stroke. Of these, 1846 (55%) and 406 (12%) experienced ischemic and hemorrhagic stroke, respectively, and in the remaining 33% it was not possible to conclusively determine the type of stroke. Our study with 43 years of follow-up (median, 30 years) generated 339329 person-years. Median baseline age, age of the first stroke, and age at death was 50, 78, and 80 years, respectively. Mean and median alcohol consumption was 4.4 and 1.6 g/d, respectively, for the entire cohort and for dizygotic pairs, and 4.6 and 1.6 g/d for complete monozygotic pairs, respectively.

Participant characteristics are presented in Table 1. High body mass index, diabetes mellitus, coronary heart disease, hypertension, smoking, stress reactivity, and being a male were associated with higher risk of stroke.

Analysis With the Entire Cohort
Initially, knowing that a J-shaped association between alcohol in grams per day and risk of stroke has been observed in previous research, the alcohol–stroke association was estimated with both linear (P=0.40) and quadratic (P=0.04) terms. The interaction between sex and alcohol (linear and quadratic) was significant (P=0.02 and P=0.001, respectively (Figure 2). After this graphical representation, the amount of alcohol consumed was categorized as described above and used in subsequent analyses.

In results adjusted for all study covariates (Table 2), alcohol consumption >24 g/d (>2 drinks/d) versus very-light consumption =0 to 5 g/d (>0.5 drink/d) was associated with 34% greater risk (P=0.02), which is comparable with risk of stroke associated with hypertension or diabetes mellitus (HR=1.41; P<0.001 and HR=1.18; P=0.002, respectively). In addition, the association between being a nondrinker and risk of stroke approached significance (HR=1.11; P=0.08). Preferred type of alcohol did not have a significant effect on risk of stroke after adjustment for all study covariates.

Results for hemorrhagic stroke suggested higher risk in all categories of alcohol drinkers, especially for heavy drinkers. In analyses run separately for men/women, risk of stroke associated with alcohol consumption >2 drinks/d was higher for women than for men (Table 2).

Age-Varying Effect of Alcohol in the Cohort
Given the potential lack of proportionality of alcohol-related stroke risk during the study period, an age-varying effect was examined with adjustment of main effects of all study covariates (Figure 3). The results show that age (measured in 5-year increments for ease of interpretation) was significantly related to increasing risk for nondrinkers (P=0.012) and decreasing risk for heavy drinkers (P=0.040). For moderate drinking, risk of stroke decreased with age with marginal significance (P=0.057). Risk of stroke for nondrinkers (versus very-light drinking) slowly increased over time and was apparent (>1) after the age of ≈70 years. Conversely, heavy drinking conferred particularly high risk of stroke (versus very-light drinking) soon after baseline median age of 50 years, and the risk decreased from young to old age, essentially reaching null at 85 years of age (when 88% of strokes in this category had already occurred). Analyses conducted separately for men and women show that moderate female drinkers have a similar risk of stroke as heavy male drinkers.

After adjustment for age-varying effects of diabetes mellitus, hypertension, and smoking, the slope of the curve representing HR of heavy drinkers (versus very-light drinkers) was less steep but remained highly clinically relevant (Figure 4). Diabetes mellitus and hypertension significantly increased stroke risk with age (measured in 5-year increments), whereas smoking had similar effect as heavy alcohol consumption.

Alcohol and Stroke in Monozygotic Twin-Pairs
In monozygotic twin-pairs discordant for stroke, twins with stroke had slightly higher alcohol consumption in comparison with twins without stroke (Table 1). In analysis of stroke discordant twin-pairs (using very-light drinkers as reference), greater (albeit nonsignificant) odds of stroke were observed for nondrinkers (odds ratio, 2.22; P=0.058), light drinkers (odds ratio, 1.56; P=0.17), moderate drinkers (odds ratio, 1.59; P=0.26), and for the 18 heavy drinkers in this analysis (odds ratio, 1.23; P=0.78). Finally, analysis of time to first stroke using concordant twin-pairs was performed. Fully adjusted results showed prolongation of time to stroke for nondrinkers by 2.07 years (P=0.11), for light drinkers by 0.77 years (P=0.54), and for moderate drinkers by 1.15 years (P=0.47) compared with very-light drinkers. The results for heavy drinkers −5.68 years (P=0.029) indicated that heavy drinking shortened time to first stroke by 5 years (compared with very-light drinkers).

Discussion
We examined midlife alcohol consumption in relation to stroke incidence during a 43-year follow-up. In line with previous research, we found that midlife alcohol consumption at >24 g/d (about >2 drinks/d on average) increased risk of stroke by 34% compared with >0 to 5 g/d (<0.5 drink/d). We also found some, although limited, support for the possibility that no consumption of alcohol may also increase the risk.

Our principal finding expanding on previous research is that the risk of stroke attributable to alcohol consumption in midlife is not the same across older adulthood, but rather is moderated by age. Our results show that risk of stroke associated with heavy drinking in midlife is at least comparable with stroke risk associated with risk factors such as diabetes.
Table 1. Characteristics of the Cohort and Subjects With or Without Stroke

<table>
<thead>
<tr>
<th>Characteristic*</th>
<th>All</th>
<th>No Stroke</th>
<th>With Stroke</th>
<th>HR (95% CI)†</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>11644</td>
<td>8316</td>
<td>3328</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Female</td>
<td>55%</td>
<td>55%</td>
<td>54%</td>
<td>0.71 (0.66–0.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age at baseline, y</td>
<td>50.5 (5.29)</td>
<td>50.4 (5.34)</td>
<td>50.9 (5.17)</td>
<td>1.00 (0.99–1.00)</td>
<td>0.502</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.4 (4.22)</td>
<td>24.3 (4.01)</td>
<td>24.6 (4.68)</td>
<td>1.02 (1.01–1.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>13%</td>
<td>12%</td>
<td>16%</td>
<td>1.33 (1.21–1.46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>25%</td>
<td>21%</td>
<td>36%</td>
<td>1.36 (1.26–1.46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>14%</td>
<td>15%</td>
<td>10%</td>
<td>1.14 (1.02–1.27)</td>
<td>0.027</td>
</tr>
<tr>
<td>Depression</td>
<td>12%</td>
<td>11%</td>
<td>14%</td>
<td>0.99 (0.89–1.09)</td>
<td>0.766</td>
</tr>
<tr>
<td>Present smoking</td>
<td>39%</td>
<td>39%</td>
<td>38%</td>
<td>1.31 (1.21–1.41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol, g/d‡</td>
<td>4.4 (7.23)</td>
<td>4.4 (7.29)</td>
<td>4.2 (7.07)</td>
<td>1.01 (1.01–1.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol drinks/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>23%</td>
<td>22%</td>
<td>24%</td>
<td>1.04 (0.96–1.13)</td>
<td>0.329</td>
</tr>
<tr>
<td>Very light (&lt;0.5 drink)</td>
<td>49%</td>
<td>49%</td>
<td>48%</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Light (0.5–1 drink)</td>
<td>18%</td>
<td>18%</td>
<td>17%</td>
<td>1.11 (1.01–1.23)</td>
<td>0.025</td>
</tr>
<tr>
<td>Moderate (1–2 drinks)</td>
<td>9%</td>
<td>9%</td>
<td>8%</td>
<td>1.22 (1.07–1.40)</td>
<td>0.003</td>
</tr>
<tr>
<td>Heavy (&gt;2 drinks)</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
<td>1.51 (1.20–1.91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not drinker</td>
<td>23%</td>
<td>22%</td>
<td>24%</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Beer</td>
<td>36%</td>
<td>36%</td>
<td>36%</td>
<td>1.05 (0.96–1.14)</td>
<td>0.308</td>
</tr>
<tr>
<td>Wine</td>
<td>22%</td>
<td>23%</td>
<td>21%</td>
<td>0.87 (0.79–0.97)</td>
<td>0.008</td>
</tr>
<tr>
<td>Spirits</td>
<td>19%</td>
<td>19%</td>
<td>18%</td>
<td>1.16 (1.04–1.29)</td>
<td>0.006</td>
</tr>
<tr>
<td>Exercise</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hardly any</td>
<td>11%</td>
<td>11%</td>
<td>12%</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Hard exercise</td>
<td>11%</td>
<td>11%</td>
<td>12%</td>
<td>1.05 (0.91–1.21)</td>
<td>0.530</td>
</tr>
<tr>
<td>Light</td>
<td>69%</td>
<td>69%</td>
<td>69%</td>
<td>0.89 (0.80–1.00)</td>
<td>0.041</td>
</tr>
<tr>
<td>Regular</td>
<td>8%</td>
<td>8%</td>
<td>7%</td>
<td>0.86 (0.73–1.02)</td>
<td>0.076</td>
</tr>
<tr>
<td>Stress reactivity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart beat</td>
<td>5%</td>
<td>4%</td>
<td>5%</td>
<td>1.29 (1.09–1.53)</td>
<td>0.003</td>
</tr>
<tr>
<td>Stomach upsets</td>
<td>8%</td>
<td>7%</td>
<td>8%</td>
<td>1.13 (0.99–1.29)</td>
<td>0.064</td>
</tr>
<tr>
<td>Throbbing headache</td>
<td>9%</td>
<td>8%</td>
<td>9%</td>
<td>1.09 (0.95–1.24)</td>
<td>0.217</td>
</tr>
<tr>
<td>&gt;1</td>
<td>6%</td>
<td>6%</td>
<td>7%</td>
<td>1.20 (1.04–1.39)</td>
<td>0.015</td>
</tr>
<tr>
<td>None of the above</td>
<td>73%</td>
<td>74%</td>
<td>72%</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Discordant MZ pairs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of subjects</td>
<td>740</td>
<td>370</td>
<td>370</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Alcohol, g/d‡</td>
<td>4.4 (7.20)</td>
<td>4.2 (7.13)</td>
<td>4.5 (7.28)</td>
<td>1.02 (1.01–1.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol drinks/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>23%</td>
<td>23%</td>
<td>23%</td>
<td>0.97 (0.80–1.18)</td>
<td>0.766</td>
</tr>
<tr>
<td>Very light (&lt;0.5 drink)</td>
<td>49%</td>
<td>50%</td>
<td>46%</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Light (0.5–1 drink)</td>
<td>18%</td>
<td>16%</td>
<td>19%</td>
<td>1.31 (1.02–1.76)</td>
<td>0.033</td>
</tr>
<tr>
<td>Moderate (1–2 drinks)</td>
<td>9%</td>
<td>7%</td>
<td>9%</td>
<td>1.72 (1.20–2.45)</td>
<td>0.003</td>
</tr>
<tr>
<td>Heavy (&gt;2 drinks)</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
<td>1.50 (0.83–2.70)</td>
<td>0.176</td>
</tr>
</tbody>
</table>

Presented statistics are counts and percentages, mean (SD) or median (Q1–Q3). Number of missing data: 349 (BMI), 11 (diabetes mellitus), 1007 (present smoking), 392 (exercise), and 1107 (stress reactivity). BMI indicates body mass index; CI, confidence interval; HR, hazard ratio; and MZ, monozygotic pairs.

*Type=preferred type of consumed alcohol.
†HR=robust Wald estimates of hazard ratios calculated using univariate Cox-regression.
‡, §Mean and median are presented for alcohol amount (‡ mean [SD], § median).
mellitus or hypertension; however, the age when those risk factors are relevant is different. The stroke risk associated with heavy drinking predominated over risk associated with these diseases early after baseline, whereas the risk associated with hypertension and diabetes mellitus grew to being more relevant at ages >75 years (for hypertension) and >80 years (for diabetes mellitus) in our study.

We also build on previous research by incorporating twin analyses with monozygotic pairs. We found that the effect of alcohol on stroke was preserved in within-pair analyses, which suggests that the stroke risk associated with alcohol is independent of genetic/early-life factors. Subsequently, analysis of concordant monozygotic twin-pairs (ie, both developed stroke, had the same genotype and were affected by the same early-life environmental factors) showed that heavy drinking (versus very-light) shortened time to stroke by ≈5 years.

Because of a relatively low number of hemorrhagic events (406 cases), we focused our analyses on the overall risk of stroke. Still, the analysis by subtype of stroke showed that risk of hemorrhagic stroke for heavy alcohol consumers is high relative to ischemic stroke. It may be that alcohol consumption could protect against ischemic stroke to some extent by improving thrombolytic profile and increasing blood flow.21

Moderate alcohol consumption (consuming 1–2 drinks/d on average) in women showed similarly harmful effect as heavy drinking (>2 drinks/d on average) in men, which is in accordance with the American Heart Association recommendations12: Men should consume no more than 2 drinks/d, and nonpregnant women should consume no more than 1 drink/d.

The strengths of this study are the 43-year follow-up, baseline at midlife, stroke diagnosis based on national registries, and opportunity to consider genetic/early-life effects. A potential limitation of our study could be a low proportion of heavy drinkers as alcohol consumption in Sweden is one of the lowest in Europe.22 However, it enabled us to explore the association between alcohol and stroke risk in a population relevant for studying a potential protective effect of alcohol. Another limitation is that data about alcohol consumption before baseline and during follow-up are not available; therefore, we can make conclusions only about the association of alcohol consumption in midlife and stroke. In addition, 20% of the sample did not have complete information on alcohol consumption, which may have compromised representativeness of the sample. Finally, hypercholesterolemia, which may be related to excessive alcohol consumption, was not controlled. However, hypertension and heart disease were.

Several sensitivity analyses have been performed to check that the exclusion of patients from analysis and the inclusion

| Table 2. Unadjusted and Adjusted Hazard Ratios (All Subjects in Cohort, Men, Women, Ischemic Stroke, and Hemorrhagic Stroke) |
|-----------|---------|-----------|---------|---------|---------|---------|
| Alcohol Drinks Consumed/d | n | None | <0.5 Drink | 0.5–1 Drink | 1–2 Drinks | >2 Drinks |
| All | Unadj | 11644 | 0.96–1.33 | Ref | 1.11* (1.01–1.23) | 1.22† (1.07–1.40) | 1.51‡ (1.20–1.91) |
| | Adj | 9487 | 0.98–1.23 | Ref | 0.98 (0.87–1.09) | 0.99 (0.85–1.15) | 1.34* (1.04–1.70) |
| Men | Unadj | 5264 | 0.89–1.25 | Ref | 1.03 (0.91–1.17) | 1.02 (0.88–1.19) | 1.19 (0.93–1.53) |
| | Adj | 4412 | 0.98–1.44 | Ref | 1.02 (0.88–1.17) | 0.99 (0.84–1.17) | 1.27‡ (0.98–1.64) |
| Women | Unadj | 6380 | 0.91–1.23 | Ref | 0.94 (0.80–1.11) | 1.00 (0.70–1.43) | 1.84‡ (0.96–3.52) |
| | Adj | 5075 | 0.89–1.19 | Ref | 0.92 (0.76–1.10) | 1.08 (0.75–1.58) | 2.02* (1.10–3.72) |
| Ischemic | Unadj | 10568 | 0.91–1.15 | Ref | 1.08 (0.95–1.23) | 1.17‡ (0.98–1.40) | 1.31 (0.95–1.82) |
| | Adj | 8629 | 0.93–1.27 | Ref | 0.97 (0.82–1.10) | 0.93 (0.75–1.12) | 1.19 (0.80–1.62) |
| Hemorrhagic | Unadj | 10568 | 0.82–1.34 | Ref | 1.17 (0.90–1.53) | 1.15 (0.79–1.68) | 1.99* (1.15–3.42) |
| | Adj | 8629 | 0.79–1.57 | Ref | 1.11 (0.80–1.51) | 1.18 (0.75–1.79) | 2.12* (1.15–3.77) |

Robust Wald estimates of hazard ratios (and 95% confidence intervals) calculated using Cox-regression are presented. Adj indicates adjusted for all study covariates; and unadj, unadjusted.

*P<0.05; †P<0.001; and ‡P≥0.05 but <0.1, otherwise the hazard ratio did not significantly differ from 1.
of transient ischemic attacks as events of interest did not significantly affect the results (detailed data not presented).

None of these analyses indicated that the results would be different: Exclusion of the 232 subjects with follow-up <5 years and the exclusion of the 3 subjects with alcohol consumption >100 g/d (as presented in Figure 1) did not affect the results. In the original analysis, 3328 stroke and transient ischemic attack events were identified. We recalculated the hazard ratios associated with alcohol consumptions where the 312 transient ischemic attack events (9% of all 3328 events) were excluded. This modification did not affect the results. Including the variable never smoker versus ever smoker instead of the variable current smoker (yes/no) did not change the results.

The number of deaths attributable to alcohol that can be considered a competing risk in relation to stroke risk was calculated. The percentage of subjects with liver cirrhosis or malignancy of the digestive system as cause of death was negligible (<1%). The most frequent cause of death to compete with stroke was cardiovascular disease, which occurred in ≈8% of the sample. Among these deaths, 8.1% of the 2622 abstainers died of cardiovascular causes, and the proportion was 7.9% of the 5874 participants in the very-light, 8.1% of 2042 in the light, 9.7% of 1000 in the moderate, and 8.8% of 306 in the heavy drinking category. Therefore, given that cardiovascular deaths increased proportionally, albeit slightly, we can conclude that cardiovascular disease is a competing risk factor with respect to the results for stroke, and that the effects of moderate or heavy alcohol drinking on risk of stroke may have been slightly greater without bias by cardiovascular deaths.

Conclusions

Heavy alcohol consumption ≥2 drinks/d on average in midlife increases stroke risk, especially shortly after baseline (on average 50 years) until the age of 75 years, and may shorten time to stroke by ≈5 years regardless of familial and other common confounds. Stroke risk associated with heavy drinking in midlife is at least comparable with stroke risk associated with risk factors such as diabetes mellitus or hypertension. The age-varying effect of alcohol on stroke enhanced the knowledge about the alcohol-stroke association. Although disease risk factors (hypertension or diabetes mellitus) increased risk of stroke predominantly in ages >75 or 80 years, respectively, the lifestyle risk factor heavy alcohol consumption (and similarly smoking) at midlife increased risk of stroke early after baseline. The results imply that alcohol consumption should be considered as a relevant age-dependent risk factor which could have application to studies of younger patients with stroke.

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Disclosures

None.

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Abstract 13

Alcohol Consumption at Midlife and Risk of Stroke During 43 Years of Follow-Up

Cohort and Twin Analyses

Pavla Kadlecová, MSc; Ross Andel, PhD; Robert Mikulik, PhD; Elizabeth P. Handing, BA; Nancy L. Pedersen, PhD

(Stroke. 2015;46:627-633.)

Key Words: alcohols ■ risk factors ■ stroke ■ twins

Figure 1. A 77-year-old man with a history of sudden onset left-sided weakness. A, Diffusion-weighted image demonstrates territorial infarctions in the right anterior and middle cerebral artery territories (arrows). Subtle susceptibility vessel signs are noted at the right M2 (B, arrowhead) and A2 (C, arrowhead) segments. D, On the arterial spin labeling image, bright vessel appearances are apparent at both the right M2 and A2 segments (arrowheads).

Figure 3. A 76-year-old man with a history of sudden onset left homonymous hemianopsia. A, Diffusion-weighted image depicts a territorial infarction in the right posterior cerebral artery (PCA) territory. B, The susceptibility vessel sign is not found within the right PCA. C, The bright vessel appearance, however, is conspicuous within the right PCA (arrow) on the arterial spin labeling image. Hypoperfusion is also noted at the infarcted area (arrowheads). D, MR angiography reveals occlusion at the right PCA (arrowhead).

중년 시기의 음주와 뇌졸중 위험성: 43년 동안 추적조사

코호트 및 쌍둥이 분석

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배경과 목적

음주와 뇌졸중의 관련성은 잘 알려져 있으나, 중년 시기의 음주가 이후 노년 시기에 발생하는 뇌졸중에 미치는 영향이 언급에 따라 달라지는지에 대해서는 아직 충분한 연구가 없다. 또한 유전/유소아 시기의 요소가 갖는 영향력에 대해서도 알려져 있지 않다. 이 연구는 뇌졸중의 발생을 43년간 추적조사한 코호트 및 쌍둥이 분석을 이용하여, 이러한 질문에 답을 하고자 하였다.

방법

스웨덴의 쌍둥이 등록 자료에 포함된, 1886년에서 1925년 사이에 출생한 11644명을 본 연구의 대상으로 하였다. 이 연구의 대상자들에 대해서는 음주력에 대한 정보가 조사되어 있었으며, 조사 당시 연령이 60세 이하이었다. 뇌졸중 발생 연령과 중년의 음주력 사이의 상호 작용은 Cox 회귀분석으로 분석하였으며, 일반성 쌍둥이 분석도 수행되었다. 공변량으로는 초기 연령, 성별, 심혈관질환, 당뇨병, 스트레스에 대한 반응, 우울증, BMI, 흡연 및 운동량이 선정되었다.

결과

例

상호관련성

Figure 1. A 77-year-old man with a history of sudden onset left-sided weakness. A, Diffusion-weighted image demonstrates territorial infarctions in the right anterior and middle cerebral artery territories (arrows). Subtle susceptibility vessel signs are noted at the right M2 (B, arrowhead) and A2 (C, arrowhead) segments. D, On the arterial spin labeling image, bright vessel appearances are apparent at both the right M2 and A2 segments (arrowheads).

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제출한

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결과

중합 29%의 대상자에서 뇌졸중이 발생하였다. 거의 승을 마시지 않는 사람(<0.5 drink/d)에 비하여 승을 많이 마시는 사람(>2 drink/d)은 뇌졸중의 위험이 높았으며(HR, 1.34; P=0.02), 승을 전혀 마시지 않는 사람은 우의성 확보에 근절한 관련성을 보았다(HR, 1.11; P=0.08). 연령은 승을 마시지 않는 사람에서 뇌졸중의 위험을 증가시켰으나(P=0.012), 승을 많이 마시는 사람은 감소시켰다(P=0.040). 승을 많이 마시는 중년의 대상자는 75세까지 대조군에 비하여 뇌졸중의 발생 위험도가 높았으나, 75세 이후에는 고혈압과 당뇨병이 더 관련있는 위험 요소가 되었다. 일반성 쌍둥이
은 중년의 과도한 음주(>2 drinks/d)와 관련된 뇌졸중 위험도는, 75세에 도달할 때까지 고혈압과 당뇨병 등 잘 알려진 뇌졸중의 위험 요소의 영향을 능가하는 것으로 밝혀졌다. 또한 과도한 음주는 공변량 및 유전/유소아 시기에 관련된 요소를 보정한 이후에도 뇌졸중이 발생하는 시기를 5년 이상 앞당겼다. 음주는 뇌졸중의 발생에 미치는 영향력이 연령에 따라 달라진다고 보아야 할 것이다.

Figure 2. Relationship between alcohol consumption and risk of stroke (J-shape model fit). Unadjusted J-shape fit of association between alcohol consumption in grams per day and stroke risk (hazard function calculated by Cox-regression model) is presented.

Figure 3. Effect of alcohol consumption in midlife on risk of stroke as a function of age. The figure presents the results adjusted for main effects of all study covariates. Individual lines represent hazard ratios for stroke as a function of age. For example, at 60 years of age risk of stroke for heavy alcohol consumers in midlife is \(2\times\) higher than for very-light drinkers (the reference group) and the risk is \(1.2\times\) higher at 80 years of age; at \(70\) years of age the risk of stroke is about the same across the low levels of midlife alcohol consumption.

Figure 4. Risk of stroke associated with alcohol consumption in midlife and with other risk factors as functions of age. The figure presents the results adjusted for main effects of all study covariates and hypertension, diabetes mellitus, and smoking as a function of age. Individual lines represent hazard ratios for stroke as a function of age: none and heavy in midlife vs very-light drinking, smokers in midlife vs nonsmokers, people with a diagnosis of diabetes mellitus or hypertension. Regardless of other risk factors, heavy drinkers had substantially higher risk of stroke than very-light drinkers in the period from baseline until the age of 90 years. Risk of stroke at baseline was \(1.05\times\) higher for patients with hypertension than for patients without hypertension and the risk was further increased with age up to hazard ratio \(=1.8\). Note that the line for moderate and light alcohol consumption, which yielded nonsignificant results, was not included to simplify the figure.