Stroke

ORIGINAL CONTRIBUTION

Drinking Patterns and Risk of Ischemic Stroke in Middle-Aged Adults

Do Beneficial Drinking Habits Indeed Exist?

Wookjin Yang, MD; Dong-Wan Kang, MD; Sue Young Ha, MD; Seung-Hoon Lee, MD, PhD

BACKGROUND AND PURPOSE: Although it has been reported that the amount of alcohol consumption has a J-shaped association with ischemic stroke, it is unclear whether differences in drinking patterns affect this relationship. We aimed to clarify the impact of drinking patterns on ischemic stroke in midlife.

METHODS: We used data from the National Health Insurance Service-National Sample Cohort, which is a large-sized, standardized population cohort in Korea. Five different drinking patterns were defined by combining the frequency of alcohol consumption and quantity of alcohol consumed per occasion, that is, abstainers, not drinking alcohol; drinker group I, ≤30 g/d and <5 d/wk; drinker group II, ≤30 g/d and ≥5 d/wk; drinker group III, >30 g/d and <5 d/wk; and drinker group IV, >30 g/d and ≥5 d/wk. The association between the drinking patterns and ischemic stroke occurrence was analyzed using the Cox proportional hazard model.

RESULTS: A total of 152 469 middle-aged participants (mean age, 50.2 years; 72 285 men [47.4%]) were eligible for the analyses. The median follow-up time was 9.0 years. Compared with abstainers, those who drank <5 d/wk (drinker groups I and III) had a significantly lower risk of ischemic stroke (group I hazard ratio, 0.71 [95% CI, 0.59–0.85]; group III hazard ratio, 0.80 [95% CI, 0.68–0.93]) during the first 7 years from the baseline, while other drinker groups showed no such differences. However, the effect of drinking patterns on ischemic stroke risk was attenuated after the first 7 years.

CONCLUSIONS: Reduced risk of ischemic stroke was observed in middle-aged participants with specific drinking patterns, but it was limited to the earlier period. Physicians should be cautious in educating patients on alcohol consumption, considering the long-term association between drinking patterns and ischemic stroke.

Key Words: alcohol drinking ■ cerebral infarction ■ drinking behavior ■ stroke

Alcohol reportedly has quite different effects on stroke depending on its subtype. While it has been consistently reported that alcohol has no protective effect on hemorrhagic stroke, a J-shaped association between drinking and ischemic stroke has been an issue of debate; modest alcohol consumption may be beneficial, whereas heavy consumption is harmful.[1–4] Previous studies have been focused primarily on the amount of alcohol consumption, analyzing either the average daily or weekly alcohol intake and have provided evidence for a reduced ischemic stroke risk with an average daily intake of <15 to 35 g.[1–5] Drinking patterns may be diverse even among individuals with similar average drinking amounts. For example, some individuals consume small amounts of alcohol with meals every day, while others do not drink often but binge once they drink. Different drinking patterns were considered in several studies on the association between alcohol and stroke, but there were certain caveats such as not distinguishing the type of stroke (hemorrhagic or ischemic)[6] or collecting alcohol consumption information only after stroke occurrence.[7]

Correspondence to: Seung-Hoon Lee, MD, PhD, Department of Neurology, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea. Email sb0516@snu.ac.kr

The Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.120.032144.

For Sources of Funding and Disclosures, see page xxx.

Stroke is available at www.ahajournals.org/journal/str

ORIGINAL CONTRIBUTION

Nonstandard Abbreviations and Acronyms

KNHANES	Korea National Health and Nutrition Examination Survey
NHIS-NSC	National Health Insurance Service-National Sample Cohort

Hence, it is necessary to more comprehensively evaluate the association between ischemic stroke risk and drinking patterns. We particularly focused on middle-aged participants in this study. Ischemic stroke is not common in younger individuals even with high alcohol consumption, owing to few vascular risk factors and good general health. In contrast, middle-aged individuals are more likely to develop vascular risk factors such as hypertension or diabetes, and consequently, ischemic stroke; in Korea, these individuals are still at a high proportion of drinking. Thus, it is worth investigating the association between drinking patterns and ischemic stroke risk in middle adulthood.

To determine the relationship between drinking patterns and ischemic stroke, we used data from the National Health Insurance Service-National Sample Cohort (NHIS-NSC) in this study. We also assessed how drinking patterns were associated with the risk of ischemic stroke over time among the middle-aged.

METHODS

All data and materials have been made publicly available at the National Health Insurance Sharing Service and can be accessed at https://nhiss.nhis.or.kr/bd/ab/bdaba000eng.do.

Study Population

The NHIS is an obligatory public health insurance service for every Korean and covers almost all medical practices performed at Korean medical institutions. The NHIS-NSC is a large-sized, representative population cohort in Korea constructed on the basis of the NHIS, which consists of 2% of Koreans randomly selected considering their demographic characteristics. Detailed information on the NHIS-NSC has been described elsewhere.[8] From this cohort, we selected participants aged 40 to 64 years, who received a general health examination at least once between 2003 and 2006. Alcohol consumption information obtained during the examination was used to define drinking patterns. Among the 164 670 qualified individuals, those with previous stroke history (N=538), missing body mass index data (N=78), and incomplete data on smoking (N=11 585) were excluded. Finally, a total of 152 469 eligible participants were analyzed. The institutional review board at the Seoul National University Hospital (institutional review board No. E-1905-104-1035) and the NHIS review committee for research support (NHIS-2019-2-215) approved the present study. The need for participant informed consent was waived.

Data Collection and Definition of Drinking Pattern

Data on sex, age at examination, height, and weight were routinely obtained for all participants. Information on hypertension, diabetes, hyperlipidemia, and atrial fibrillation was collected as per the *International Classification of Disease*, *Tenth Revision* codes from the NHIS-NSC medical treatment database. Data on alcohol intake were collected at baseline through a questionnaire using the quantity-frequency method, which estimated the frequency and amount of alcohol consumption. The drinking amount was surveyed based on a type of distilled beverage called Soju.[8] It is the most commonly consumed alcoholic beverage in Korea which contains ≈60 g of alcohol/bottle (Tables I and II in the Data Supplement).[9,10] Participants were asked to choose a single answer to questions on drinking frequency and amount among several choices—drinking frequency: never, 2 to 3/mo, 1 to 2/wk, 3 to 4/wk, almost daily; drinking amount per occasion: ≤0.5 bottle, 1 bottle, 1.5 bottles, ≥2 bottles of Soju.[8] To assess the validity of the alcohol consumption measurements, we compared our data with the Korea National Health and Nutrition Examination Survey (KNHANES) data, which provide the official health care statistics data.[11,12] We grouped our study population as per definitions used in the KNHANES II (current drinkers, participants except abstainers; risky drinkers, daily consumption ≥40 g and frequency ≥1/wk; and high-risk drinkers, daily consumption ≥40 g and frequency ≥3/wk), and compared proportions of these groups in the 2 databases by sex and age. The classifications of risky and high-risk drinkers for our study population were based on >30 g/d instead of ≥40 g/d as per the KNHANES II.

In this study, drinking patterns were defined by combining weekly drinking frequency and consumption per occasion. Despite some variations, most countries now recommend a daily alcohol consumption of no more than 20 to 40 g for men and 10 to 40 g for women (Table III in the Data Supplement).[13] Based on these global guidelines, we set 30 grams of alcohol (equivalent to half a bottle of Soju) as the threshold consumption value for grouping participants. The drinking frequency categories were defined as <5 d/wk and ≥5 d/wk. Accordingly, we defined 5 drinking patterns: abstainers, not drinking alcohol; drinker group I, ≤30 g/d and <5 d/wk; drinker group II, ≤30 g/d and ≥5 d/wk; drinker group III, >30 g/d and <5 d/wk; and drinker group IV, >30 g/d and ≥5 d/wk. Smoking status and physical activity were also reported through the questionnaire. We defined regular exercise as exercising ≥3 d/wk. From income levels divided by deciles, socioeconomic status was categorized into 3 groups (lower 30%, middle 40%, and upper 30%).

Identification of Ischemic Stroke

The first incident ischemic stroke occurred in the period from the baseline examination to the last day of 2013 was the main outcome of interest in the present study. The *International Classification of Disease, Tenth Revision* code (ischemic stroke, I63.X) recorded in the cohort was used to identify ischemic stroke. Patients who had been admitted with the code were regarded to have incident ischemic stroke in this study. Transient ischemic attack was excluded. It is mandatory for all Korean citizens to join the NHIS, as described earlier. The

NHIS collects health insurance premiums from the participants and pays the premiums to hospitals. Since medical procedure costs in hospitals are borne by the NHIS, this organization has precise data on admission, diagnosis, and medical examination of all Koreans.[8] Therefore, data on *International Classification of Disease, Tenth Revision* diagnosis at admission in the NHIS-NSC allowed for accurate determination of the incidence of ischemic stroke. In a validation study conducted using NHIS claims, defining ischemic stroke using the *International Classification of Disease, Tenth Revision* code had a sensitivity of 67% to 83%, a specificity of 84% to 97%, and a positive predictive value of 89% to 95%.[14]

Statistical Methods

Baseline parameters were analyzed using 1-way ANOVA and the χ^2 test, as appropriate. The Bonferroni method was used to perform pairwise comparisons of baseline parameters among groups based on drinking patterns. Because age was recorded as age groups of 5 years in the cohort, it was transformed to a numeric variable by adopting the median value in each group. To compare the proportions of drinker groups between the KNHANES data set and our study's data set, the χ^2 test and Fisher exact test were used, as appropriate. The Cox proportional hazard model was used to evaluate the hazard ratios for incident ischemic stroke according to drinking pattern. Proportional hazard assumptions were assessed through scaled Schoenfeld residuals. If the proportional hazard assumption was not fulfilled, a step function was used to assess effects of the time-varying variable over divided time intervals. Thus, we split the analysis time into 2 intervals and fitted the stratified Cox model for each time interval. The split point was selected by visual inspection of the scaled Schoenfeld residual plot for the variable with a time-dependent coefficient.[15] Death and emigration were regarded as censoring events in our study. Age and sex were first adjusted, and additional adjustments for the following factors were performed subsequently: body mass index, hypertension, diabetes, hyperlipidemia, atrial fibrillation, smoking status, regular exercise, and socioeconomic status. To evaluate whether exclusion of the 11 585 participants with incomplete data on smoking status may have affected the results of the present study, multivariable analyses with adjustments for the aforementioned factors except for smoking status were performed in the populations with and without these additional participants. To assess whether the effect of drinking pattern was different by sex or age groups (early middle-aged, 40–49 years; late middle-aged, 50–64 years), subgroup analyses were performed using Cox proportional hazard models. The results were described as hazard ratios with their 95% CIs. Two-sided probability values <0.05 were considered statistically significant. Statistical analyses were performed using the R statistical software (v3.6.0, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The mean (SD) age of the participants was 50.2 (7.1) years, and 47.4% were men (N=72 285), among a total of 152 469 eligible participants. The proportions of current drinker and risky drinker groups by sex and age were comparable between our study data and the KNHANES data. However, proportions of some groups (female current drinkers aged 40–49 years and male high-risk drinkers) tended to be a little under-reported in this study (Table IV in the Data Supplement).

Table 1 illustrates the demographic characteristics and stroke risk factors of the participants by drinking pattern. Of the 5 delineated groups, there were more women, never smokers, and participants with hyperlipidemia in the abstainer group, than in the drinker groups. No difference in blood pressure was observed between abstainers and drinker group I though the proportion of hypertensive participants was higher in the abstainer group. When analyzed by the presence of hypertension diagnosis, drinker group I showed higher blood pressure values compared with abstainers with hypertension (abstainers: mean systolic blood pressure, 135.6; SD, 18.5 versus drinker group I: mean, 136.9; SD, 18.8; $P<0.001$) and without hypertension (abstainers: mean, 120.7; SD, 15.6 versus drinker group I: mean, 121.5; SD, 15.6; $P<0.001$). Among drinkers, group IV had the highest proportions of hypertensive and diabetic participants notwithstanding the failure to show a significant difference from drinker group II. Drinker group III tended to be the youngest and at the highest income level among the 5 groups. Results of pairwise comparisons between groups as per drinking pattern are presented in Table V in the Data Supplement.

During a median follow-up period of 9.0 years (interquartile range, 8.0–10.0 years), there were 1960 incident ischemic strokes. Among variables included in the analysis, drinking pattern, specifically drinker group I did not fulfill the proportional hazard assumption for the Cox proportional hazard model ($P=0.02$). Since the log hazard ratio for drinker group I crossed zero at around 7 years (Figure I in the Data Supplement), we divided the data set into 2 time intervals: first 7 years and after 7 years from the baseline. The divided data sets did not violate the proportional hazard assumption.

In this study, drinking patterns influenced ischemic stroke risk in the middle-aged, though the risk varied based on time interval from baseline examination. Those who drank less frequently (drinker groups I and III) showed a lower ischemic stroke risk than did the abstainers, whereas no difference was found between drinker groups II and IV and abstainers during the first 7 years. During the latter follow-up period, ischemic stroke risk was higher in drinker group IV than in abstainers, but other drinker groups showed no significant difference (Figure 1, Tables 2 and 3). Although a proportion of participants were excluded in the main analysis owing to incomplete data on smoking status, the results of the analyses with and without the additional inclusion of these cases showed similar trends (Tables VI and VII in the Data Supplement).

ORIGINAL CONTRIBUTION

Table 1. Baseline Characteristics According to Drinking Pattern

Variable	Abstainer (N=90 373)	Drinker group I (N=23 126)*	Drinker group II (N=1456)*	Drinker group III (N=33 302)*	Drinker group IV (N=4212)*	*P* value
Male sex, N (%)	25 813 (28.6)	11 691 (50.6)	1104 (75.8)	29 664 (89.1)	4013 (95.3)	<0.001
Age, mean (SD), y	51.0 (7.2)	49.6 (6.9)	53.6 (7.2)	48.3 (6.4)	51.5 (7.1)	<0.001
Body mass index, mean (SD), kg/m^2	23.9 (3.0)	23.7 (2.8)	23.5 (2.8)	24.3 (2.8)	24.0 (3.0)	<0.001
Systolic blood pressure, mean (SD), mm Hg	123.6 (17.3)	123.9 (17.1)	128.7 (18.6)	127.8 (16.8)	131.9 (17.9)	<0.001
Hypertension, N (%)	17 495 (19.4)	3607 (15.6)	254 (17.4)	5479 (16.5)	800 (19.0)	<0.001
Diabetes, N (%)	8730 (9.7)	1565 (6.8)	129 (8.9)	2795 (8.4)	437 (10.4)	<0.001
Hyperlipidemia, N (%)	8454 (9.4)	1662 (7.2)	87 (6.0)	2409 (7.2)	313 (7.4)	<0.001
Atrial fibrillation, N (%)	358 (0.4)	75 (0.3)	7 (0.5)	100 (0.3)	14 (0.3)	0.09
Smoking status, N (%)						<0.001
Nonsmoker	80 622 (89.2)	16 026 (69.3)	693 (47.6)	12 020 (36.1)	1121 (26.6)	
Ex-smoker	1583 (1.8)	1171 (5.1)	100 (6.9)	3183 (9.6)	288 (6.8)	
Current smoker	8168 (9.0)	5929 (25.6)	663 (45.5)	18 099 (54.3)	2803 (66.5)	
Regular exercise, N (%)	17 461 (19.3)	5129 (22.2)	302 (20.7)	7320 (22.0)	846 (20.1)	<0.001
Socioeconomic status, N (%)†						<0.001
0–29th percentile, lowest	20 987 (23.2)	5351 (23.1)	349 (24.0)	5780 (17.4)	890 (21.1)	
30th–69th percentile	31 044 (34.4)	7615 (32.9)	643 (44.2)	11 251 (33.8)	1853 (44.0)	
70th–100th percentile	38 342 (42.4)	10 160 (43.9)	464 (31.9)	16 271 (48.9)	1469 (34.9)	

*Drinker group I, ≤30 g/d and <5 d/wk; drinker group II, ≤30 g/d and ≥5 d/wk; drinker group III, >30 g/d and <5 d/wk; and drinker group IV, >30 g/d and ≥5 d/wk.
†The socioeconomic status was classified into 3 groups based on income deciles: lower 30%, middle 40%, and upper 30%.

When analyzed by sex or age group, the association between drinking pattern and ischemic stroke in men and late middle-aged participants showed similar trends with the findings in the total population. However, in the early middle-aged group, the hazards of drinker groups were generally higher after the first 7 years compared with abstainers; results for drinker groups II and IV were inconclusive owing to small event numbers. Female participants of drinker group II had an increased risk of ischemic stroke in the earlier period; however, results were unreliable owing to small event numbers in women from drinker groups II and IV (Figure 2, Tables VIII–XI in the Data Supplement).

DISCUSSION

The risk of ischemic stroke in midlife varied according to drinking pattern in this study, but this association changed over follow-up time from baseline examination. Drinking more alcohol at once and less frequently (drinker group III) conferred a lower ischemic stroke risk than did abstaining, while drinking less alcohol more frequently (drinker group II) did not lower risk during the first 7 years. However, alcohol consumption was not associated with a reduced risk regardless of drinking pattern in a long-term perspective; no favorable association was observed even in participants with the lowest consumption (drinker group I) as well as drinker group III, after the first 7 years.

Previous studies have been focused primarily on consumption levels while disregarding drinking patterns.[1–5] In this study, we assessed the association between ischemic stroke risk and drinking patterns because drinking patterns may differ among individuals. Drinking patterns may reflect individuals' lifestyles and social behaviors; additionally, alcohol is a quite important nonverbal communication tool for improving social relationships in Korea.[16] In a Korean domestic survey study with 1185 participants, participants reported drinking more often with friends/colleagues rather than by themselves. Consumption per occasion was higher when participants drank with friends/colleagues than when they drank alone. Also, approximately one-third of the subjects reported their experiences of reluctant participation and unwilling excessive drinking while in groups.[17] A proportion of the group III drinkers in our study may fall into this category of unwilling drinkers. Socioeconomic status may also explain the lower ischemic stroke risk in group III compared with group II drinkers. In previous studies, a high socioeconomic status was linked to moderate drinking,[18] while a low socioeconomic status signified an increased risk of alcohol dependence and of alcohol-related hospitalization or death even at comparable drinking levels.[19,20] The proportion of high socioeconomic status participants in our study was highest in the drinker group III, whereas that of low socioeconomic status participants was highest in drinker group II. Group III drinkers may have advantages in maintaining good health

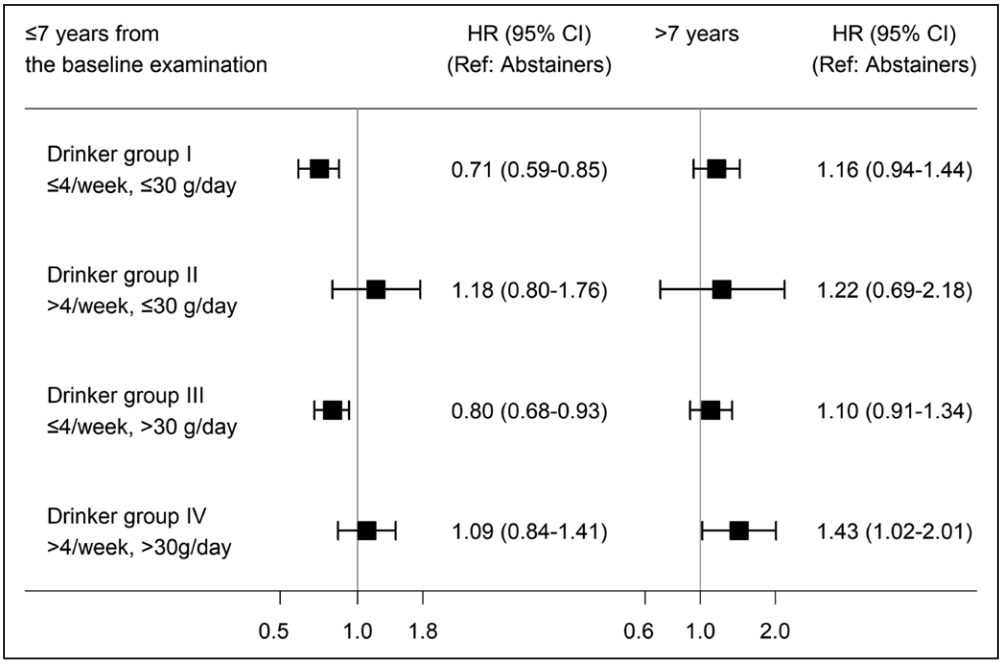

Figure 1. Risk of incident ischemic stroke according to drinking pattern.
Hazard ratios (HRs) for ischemic stroke for each drinking pattern. The abstainers were set as the reference group. Horizontal lines indicate the 95% CIs. The HRs were adjusted for the variables in model II as shown in Table 2. The HRs were plotted on a log scale.

attributed to higher socioeconomic status (better vascular risk factor control, recognizing the harm of alcohol, and preventing alcohol dependence), and this might have led to better outcomes during the earlier period.

Low-to-moderate alcohol consumption, defined as an average daily consumption of 1 to 3 drinks by previous studies, reportedly has protective effects for ischemic stroke.[1–5] In accordance with the previous studies, the lowest consumption group (drinker group I) in this study showed a lower ischemic stroke risk, compared with abstainers. However, this association was attenuated in the latter follow-up period: drinker group I no longer had a favorable outcome after the first 7 years. Hence, the protective effect of low-risk drinking on ischemic stroke reported previously might be diminished over time. In recent studies, low-to-moderate drinking as well as heavy drinking increased blood pressure and hypertension risk, especially in men.[21–24] Therefore, even at a

Table 2. Hazard Ratios for Incident Ischemic Stroke by Drinking Patterns, During the First 7 Years From Baseline Examination

	1–4/wk	5–7/wk
≤30 g/d	Drinker group I (N=23 126)	Drinker group II (N=1456)
Ischemic stroke, N (%)	145 (0.6)	26 (1.8)
Unadjusted HR	0.74 (0.62–0.88)	2.14 (1.45–3.16)
Model I*	0.71 (0.60–0.85)	1.20 (0.81–1.78)
Model II†	0.71 (0.59–0.85)	1.18 (0.80–1.76)
>30 g/d	Drinker group III (N=33 302)	Drinker group IV (N=4212)
Ischemic stroke, N (%)	263 (0.8)	68 (1.6)
Unadjusted HR	0.93 (0.81–1.07)	1.94 (1.52–2.49)
Model I	0.90 (0.77–1.05)	1.25 (0.97–1.62)
Model II	0.80 (0.68–0.93)	1.09 (0.84–1.41)

Reference group: Abstainers (N=90 373; 764 [0.8%] ischemic strokes). HR indicates hazard ratio.
*Model I: adjusted for age and sex.
†Model II: model I+body mass index, hypertension, diabetes, hyperlipidemia, atrial fibrillation, smoking status, regular exercise, and socioeconomic status.

Table 3. Hazard Ratios for Incident Ischemic Stroke by Drinking Patterns, After the First 7 Years From Baseline Examination

	1–4/wk	5–7/wk
≤30 g/d	Drinker group I (N=20 033)	Drinker group II (N=1210)
Ischemic stroke, N (%)	112 (0.6)	12 (1.0)
Unadjusted HR	1.20 (0.97–1.49)	2.19 (1.23–3.89)
Model I*	1.17 (0.94–1.45)	1.23 (0.69–2.20)
Model II†	1.16 (0.94–1.44)	1.22 (0.69–2.18)
>30 g/d	Drinker group III (N=28 560)	Drinker group IV (N=3494)
Ischemic stroke, N (%)	171 (0.6)	39 (1.1)
Unadjusted HR	1.29 (1.07–1.54)	2.51 (1.80–3.49)
Model I	1.25 (1.03–1.51)	1.66 (1.18–2.32)
Model II	1.10 (0.91–1.34)	1.43 (1.02–2.01)

Reference group: Abstainers (N=77 680; 360 [0.5%] ischemic strokes). HR indicates hazard ratio.
*Model I: adjusted for age and sex.
†Model II: model I+body mass index, hypertension, diabetes, hyperlipidemia, atrial fibrillation, smoking status, regular exercise, and socioeconomic status.

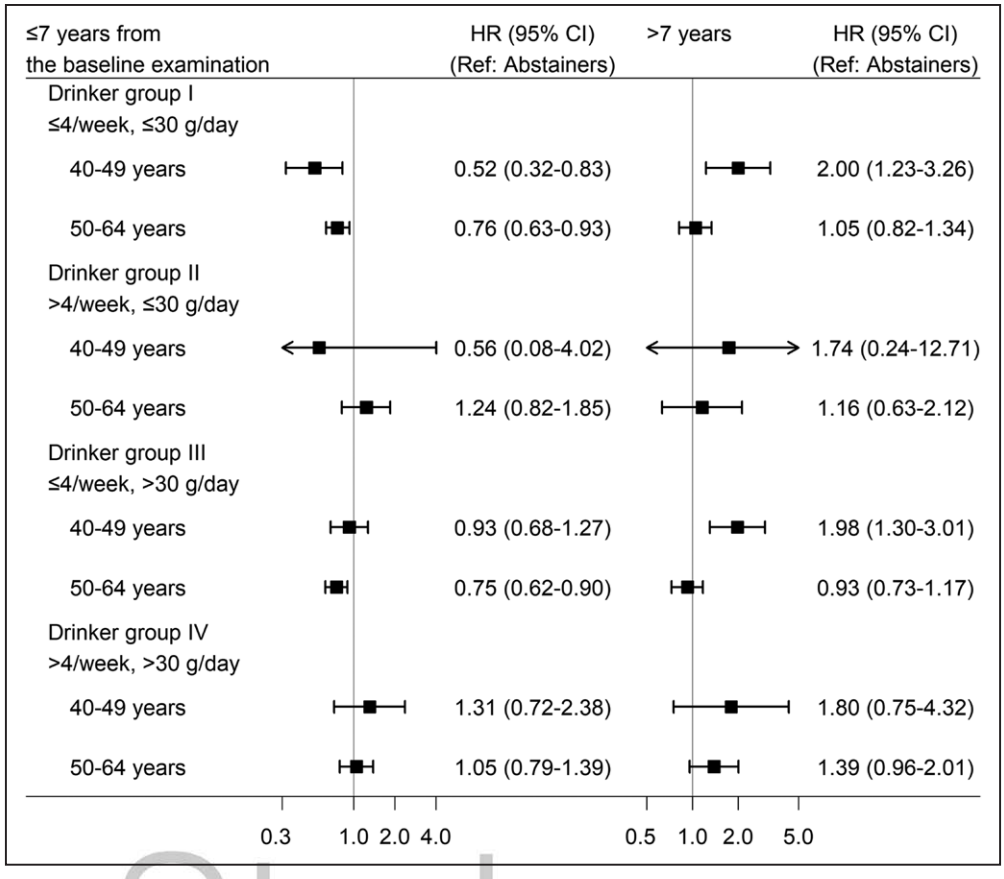

Figure 2. Risk of incident ischemic stroke separately analyzed by age group.
Hazard ratios (HR) for ischemic stroke for each drinking pattern were separately analyzed by age group. The abstainers were set as the reference group. Horizontal lines indicate the 95% CIs. The HRs were adjusted for the variables in model II as shown in Table 2. The HRs were plotted on a log scale.

low consumption level, alcohol may be detrimental with respect to hypertension, which is a major ischemic stroke risk factor. The incidence of hypertension was lowest in drinker group I, though the actual blood pressure value of this group was higher than that of abstainers. Drinker group I, which corresponds to the low-to-moderate drinkers in previous reports, may also be at an increased risk of future hypertension compared with abstainers. On the contrary, it has been reported that alcohol may lower fibrinogen, elevate tissue plasminogen activator, and inhibit platelet activity, leading to antithrombic effects.[25–30] Perhaps moderate amounts of alcohol consumption might have effects similar to those of antithrombotic drugs and thus may be protective against ischemic stroke. In other words, alcohol may have both beneficial and harmful effects on vascular health. The time-varying effects of drinking patterns may be attributed to the ambivalent effects of alcohol on ischemic stroke risk. Thus, alcohol consumption of group I drinkers may induce antithrombotic effects similar to taking antithrombotic drugs, while it may simultaneously increase the risk of under-controlled hypertension. Antithrombotic effects may prevent ischemic stroke in the early stages; however, ischemic stroke risk may rise over time with accumulated damage caused by risk factors, such as hypertension. Given that the elderly are more vulnerable to the damages of alcohol than younger adults,[31] the harmful effects of alcohol would be more pronounced in the latter period as the participants age. In the same fashion, ischemic stroke risk was not different in drinker group IV (participants with high drinking amount and frequency) compared with abstainers in the earlier period but was elevated in the long-term. In addition, early middle-aged drinkers displayed a higher ischemic stroke risk than did abstainers during long-term follow-up. The incidence of ischemic stroke risk factors at baseline may be lower in early middle-aged compared with late middle-aged participants. Thus, ischemic stroke risk might be influenced less by existing risk factors and better reflect the effects of alcohol itself on ischemic stroke.

Although detailed information on the type of beverage was not included in our database, Soju, a type of distilled spirit, accounts for the majority of alcohol consumed in Korea (Tables I and II in the Data Supplement).[9,10] It contains almost no nutrients, minerals, or other nonalcoholic compounds beneficial to health, as opposed to fermented beverages, such as wine or beer.[32] The cumulative effect of pure alcohol without additional

health benefits from these nonalcoholic contents might play some role in the attenuation of risk reduction in the latter period, considering that fermented beverages reportedly conferred lower risks of ischemic stroke and other cardiovascular diseases compared with spirits at a similar consumption level.[33,34]

There are several limitations to our study. First, alcohol consumption data were based on self-reports and the risk of under-reporting should be acknowledged. Under-reporting is an unavoidable issue in self-report-based alcohol-related data. Indeed, alcohol intake data collected in this study tended to be under-reported in some parts compared with official statistical data. However, in real-world clinical situations, physicians discuss ischemic stroke prevention and obtain alcohol consumption information by querying how often and how much alcohol is consumed by the patient. This manner of querying is comparable to that of the self-reported questionnaires used in this study. Therefore, our study results might be better applied to actual clinical practice in which drinking information is obtained by asking patients simple questions. Second, residual confounding factors may have affected the results of our study. Compared with men, women are reported to achieve higher peak blood alcohol levels after drinking the same amount of alcohol, and be more susceptible to alcohol-related organ injuries.[35,36] This may affect the association between drinking patterns and ischemic stroke. However, sex-differences were not fully considered in this study as drinking patterns were classified by the same criteria in both sexes. Factors influencing the absorption, distribution, and metabolism of alcohol such as food intake, dietary patterns, and type of alcoholic beverage could not be handled in this study due to database limitations. Third, the results of the present study were based on a 1-time assessment of drinking behavior at baseline. Although drinking habits of participants might change over time, it was not considered in our study, and the results should be cautiously interpreted. Finally, though drinking patterns, amount, and type of popular liquor vary by country and ethnicity, this study only included Koreans, although the cohort was carefully standardized.

To date, the beneficial effects of moderate drinking on ischemic stroke have been accepted as an almost established conclusion among stroke physicians, based on the studies focused primarily on the amount of alcohol consumption. Our results imply that alcohol may be differently associated with ischemic stroke risk based on drinking patterns as well as on consumption levels, and that favorable associations of specific drinking patterns on ischemic stroke might be transient in midlife. This study thus may have raised a new issue to discuss, the time-varying effects of drinking patterns on ischemic stroke risk. Although it is not possible to draw a novel conclusion based on this single study alone, it may now be necessary to pay attention on this consolidated topic again.

ARTICLE INFORMATION

Received August 7, 2020; final revision received September 13, 2020; accepted October 1, 2020.

Affiliations

Department of Neurology, Seoul National University Hospital, Republic of Korea (W.Y., D.-W.K., S.Y.H., S.-H.L.). The Korean Cerebrovascular Research Institute, Seoul, Republic of Korea (W.Y., D.-W.K., S.-H.L.).

Sources of Funding

This work was supported by the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI) funded by the Ministry of Health & Welfare, Republic of Korea [HI17C0076], and the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science and ICT [NRF-2018R1A2A2A05022369].

Disclosures

None.

Supplemental Materials

Figure I
Tables I–XI

REFERENCES

1. Patra J, Taylor B, Irving H, Roerecke M, Baliunas D, Mohapatra S, Rehm J. Alcohol consumption and the risk of morbidity and mortality for different stroke types–a systematic review and meta-analysis. *BMC Public Health*. 2010;10:258. doi: 10.1186/1471-2458-10-258
2. Reynolds K, Lewis B, Nolen JD, Kinney GL, Sathya B, He J, Lewis BL. Alcohol consumption and risk of stroke: a meta-analysis. *JAMA*. 2003;289:579–588. doi: 10.1001/jama.289.5.579
3. Larsson SC, Wallin A, Wolk A, Markus HS. Differing association of alcohol consumption with different stroke types: a systematic review and meta-analysis. *BMC Med*. 2016;14:178. doi: 10.1186/s12916-016-0721-4
4. Zhang C, Qin YY, Chen Q, Jiang H, Chen XZ, Xu CL, Mao PJ, He J, Zhou YH. Alcohol intake and risk of stroke: a dose-response meta-analysis of prospective studies. *Int J Cardiol*. 2014;174:669–677. doi: 10.1016/j.ijcard.2014.04.225
5. Ronksley PE, Brien SE, Turner BJ, Mukamal KJ, Ghali WA. Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis. *BMJ*. 2011;342:d671. doi: 10.1136/bmj.d671
6. Wannamethee SG, Shaper AG. Patterns of alcohol intake and risk of stroke in middle-aged British men. *Stroke*. 1996;27:1033–1039. doi: 10.1161/01.str.27.6.1033
7. Palomäki H, Kaste M. Regular light-to-moderate intake of alcohol and the risk of ischemic stroke. Is there a beneficial effect? *Stroke*. 1993;24:1828–1832. doi: 10.1161/01.str.24.12.1828
8. Lee J, Lee JS, Park SH, Shin SA, Kim K. Cohort profile: The National Health Insurance Service-National Sample Cohort (NHIS-NSC), South Korea. *Int J Epidemiol*. 2017;46:e15. doi: 10.1093/ije/dyv319
9. World Health Organization. Global status report on alcohol and health 2018. https://www.who.int/publications-detail/global-status-report-on-alcohol-and-health-2018. Accessed March 25, 2020.
10. 2018 Alcohol Statistics. Korea Health Promotion Institution. https://www.khealth.or.kr/fileDownload?titleId=30400&fileId=1&fileDownType=C. Accessed March 24, 2020.
11. Kweon S, Kim Y, Jang MJ, Kim Y, Kim K, Choi S, Chun C, Khang YH, Oh K. Data resource profile: the Korea National Health and Nutrition Examination Survey (KNHANES). *Int J Epidemiol*. 2014;43:69–77. doi: 10.1093/ije/dyt228
12. Choi JS. The Korea National Health and Nutrition Examination Survey II–health survey. *Ministry of Health and Welfare, Republic of Korea*. 2003.
13. Drinking guidelines: General population. International Alliance for Responsible Drinking (IARD). https://iard.org/science-resources/detail/Drinking-Guidelines-General-Population. Accessed July 4, 2020.

14. Park TH, Choi JC. Validation of stroke and thrombolytic therapy in Korean national health insurance claim data. *J Clin Neurol*. 2016;12:42–48. doi: 10.3988/jcn.2016.12.1.42
15. Therneau T, Crowson C, Atkinson E. Using time dependent covariates and time dependent coefficients in the Cox model. R package Survival Vignettes. https://cran.r-project.org/web/packages/survival/vignettes/timedep.pdf. Accessed April 8, 2020.
16. Chun S. The social meaning of alcohol consumption in Korea. *J Korean Diabetes* 2012;13:57–60.
17. Ko S, Sohn A. Behaviors and culture of drinking among Korean people. *Iran J Public Health*. 2018;47(suppl 1):47–56.
18. Lee SJ, Sudore RL, Williams BA, Lindquist K, Chen HL, Covinsky KE. Functional limitations, socioeconomic status, and all-cause mortality in moderate alcohol drinkers. *J Am Geriatr Soc*. 2009;57:955–962. doi: 10.1111/j.1532-5415.2009.02184.x
19. Fazel S, Khosla V, Doll H, Geddes J. The prevalence of mental disorders among the homeless in western countries: systematic review and meta-regression analysis. *PLoS Med*. 2008;5:e225. doi: 10.1371/journal.pmed.0050225
20. Katikireddi SV, Whitley E, Lewsey J, Gray L, Leyland AH. Socioeconomic status as an effect modifier of alcohol consumption and harm: analysis of linked cohort data. *Lancet Public Health*. 2017;2:e267–e276. doi: 10.1016/S2468-2667(17)30078-6
21. O'Keefe EL, DiNicolantonio JJ, O'Keefe JH, Lavie CJ. Alcohol and CV health: Jekyll and Hyde J-curves. *Prog Cardiovasc Dis*. 2018;61:68–75. doi: 10.1016/j.pcad.2018.02.001
22. Zhao PP, Xu LW, Sun T, Wu YY, Zhu XW, Zhang B, Cheng Z, Cai X, Liu YC, Zhao TT, et al. Relationship between alcohol use, blood pressure and hypertension: an association study and a Mendelian randomisation study. *J Epidemiol Community Health*. 2019;73:796–801. doi: 10.1136/jech-2018-211185
23. Taylor B, Irving HM, Baliunas D, Roerecke M, Patra J, Mohapatra S, Rehm J. Alcohol and hypertension: gender differences in dose-response relationships determined through systematic review and meta-analysis. *Addiction*. 2009;104:1981–1990. doi: 10.1111/j.1360-0443.2009.02694.x
24. Briasoulis A, Agarwal V, Messerli FH. Alcohol consumption and the risk of hypertension in men and women: a systematic review and meta-analysis. *J Clin Hypertens (Greenwich)*. 2012;14:792–798. doi: 10.1111/jch.12008
25. Chiva-Blanch G, Badimon L. Benefits and risks of moderate alcohol consumption on cardiovascular disease: current findings and controversies. *Nutrients*. 2019;12:108. doi: 10.3390/nu12010108
26. Stote KS, Tracy RP, Taylor PR, Baer DJ. The effect of moderate alcohol consumption on biomarkers of inflammation and hemostatic factors in postmenopausal women. *Eur J Clin Nutr*. 2016;70:470–474. doi: 10.1038/ejcn.2015.182
27. Brien SE, Ronksley PE, Turner BJ, Mukamal KJ, Ghali WA. Effect of alcohol consumption on biological markers associated with risk of coronary heart disease: systematic review and meta-analysis of interventional studies. *BMJ*. 2011;342:d636. doi: 10.1136/bmj.d636
28. Ridker PM, Vaughan DE, Stampfer MJ, Glynn RJ, Hennekens CH. Association of moderate alcohol consumption and plasma concentration of endogenous tissue-type plasminogen activator. *JAMA*. 1994;272:929–933. doi: 10.1001/jama.1994.03520120039028
29. Smith S, Fair K, Goodman A, Watson J, Dodgion C, Schreiber M. Consumption of alcohol leads to platelet inhibition in men. *Am J Surg*. 2019;217:868–872. doi: 10.1016/j.amjsurg.2019.02.020
30. Mukamal KJ, Massaro JM, Ault KA, Mittleman MA, Sutherland PA, Lipinska I, Levy D, D'Agostino RB, Tofler GH. Alcohol consumption and platelet activation and aggregation among women and men: the Framingham Offspring study. *Alcohol Clin Exp Res*. 2005;29:1906–1912. doi: 10.1097/01.alc.0000183011.86768.61
31. Kim JW, Lee DY, Lee BC, Jung MH, Kim H, Choi YS, Choi IG. Alcohol and cognition in the elderly: a review. *Psychiatry Investig*. 2012;9:8–16. doi: 10.4306/pi.2012.9.1.8
32. Ryu HY, Kum EJ, Bae KH, Kim YK, Kwun IS, Sohn HY. Evaluation for the antimicrobial, antioxidant and anti-thrombosis activity of Korean traditional liquors. *Korean J Microbiol Biotechnol*. 2007;35:238–244.
33. Malarcher AM, Giles WH, Croft JB, Wozniak MA, Wityk RJ, Stolley PD, Stern BJ, Sloan MA, Sherwin R, Price TR, et al. Alcohol intake, type of beverage, and the risk of cerebral infarction in young women. *Stroke*. 2001;32:77–83. doi: 10.1161/01.str.32.1.77
34. Costanzo S, Di Castelnuovo A, Donati MB, Iacoviello L, de Gaetano G. Wine, beer or spirit drinking in relation to fatal and non-fatal cardiovascular events: a meta-analysis. *Eur J Epidemiol*. 2011;26:833–850. doi: 10.1007/s10654-011-9631-0
35. Ramchandani VA, Bosron WF, Li TK. Research advances in ethanol metabolism. *Pathol Biol (Paris)*. 2001;49:676–682. doi: 10.1016/s0369-8114(01)00232-2
36. Sato N, Lindros KO, Baraona E, Ikejima K, Mezey E, Järveläinen HA, Ramchandani VA. Sex difference in alcohol-related organ injury. *Alcohol Clin Exp Res*. 2001;25(5 Suppl ISBRA):40S–45S. doi: 10.1097/00000374-200105051-00007