Alcohol use and risk of intracerebral hemorrhage

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ABSTRACT

Objective: To analyze the dose-risk relationship for alcohol consumption and intracerebral hemorrhage (ICH) in the Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) study.

Methods: ERICH is a multicenter, prospective, case-control study, designed to recruit 1,000 non-Hispanic white patients, 1,000 non-Hispanic black patients, and 1,000 Hispanic patients with ICH. Cases were matched 1:1 to ICH-free controls by age, sex, race/ethnicity, and geographic area. Comprehensive interviews included questions regarding alcohol consumption. Patterns of alcohol consumption were categorized as none, rare (<1 drink per month), moderate (≥ 1 drink per month and ≤ 2 drinks per day), intermediate (>2 drinks per day and <5 drinks per day), and heavy (≥ 5 drinks per day). ICH risk was calculated using the no-alcohol use category as the reference group.

Results: Multivariable analyses demonstrated an ordinal trend for alcohol consumption: rare (odds ratio [OR] 0.57, $p < 0.0001$), moderate (OR 0.65, $p < 0.0001$), intermediate (OR 0.82, $p = 0.2666$), and heavy alcohol consumption (OR 1.77, $p = 0.0003$). Subgroup analyses demonstrated an association of rare and moderate alcohol consumption with decreased risk of both lobar and nonlobar ICH. Heavy alcohol consumption demonstrated a strong association with increased nonlobar ICH risk (OR 2.04, $p = 0.0003$). Heavy alcohol consumption was associated with significant increase in nonlobar ICH risk in black (OR 2.34, $p = 0.0140$) and Hispanic participants (OR 12.32, $p < 0.0001$). A similar association was not found in white participants.

Conclusions: This study demonstrated potential protective effects of rare and moderate alcohol consumption on ICH risk. Heavy alcohol consumption was associated with increased ICH risk. Race/ethnicity was a significant factor in alcohol-associated ICH risk; heavy alcohol consumption in black and Hispanic participants poses significant nonlobar ICH risk. **Neurology® 2017;88:2043-2051**

GLOSSARY

BMI = body mass index; **BP** = blood pressure; **CAD** = coronary artery disease; **CI** = confidence interval; **DM** = diabetes mellitus; **ERICH** = Ethnic/Racial Variations of Intracerebral Hemorrhage; **HDL** = high-density lipoprotein; **ICH** = intracerebral hemorrhage; **INR** = international normalized ratio; **LDL** = low-density lipoprotein; **MI** = myocardial infarction; **mRS** = modified Rankin Scale; **OR** = odds ratio; **PT** = prothrombin time; **PTT** = partial thromboplastin time; **RR** = relative risk.

The relationship between alcohol consumption and stroke is complex. A U-shaped relationship has been identified between alcohol consumption and ischemic stroke, whereas a more linear relationship has been found between alcohol use and hemorrhagic stroke.¹⁻³ Despite the identification of alcohol consumption as a consistent risk factor for intracerebral hemorrhage (ICH), the dose-dependent relationship between alcohol consumption and ICH remains unclear.⁴⁻⁷ The effects of alcohol may vary among different race/ethnic groups with potential differences in alcohol consumption thresholds for increased ICH risk. Alcohol consumption is associated with hypertension, and may have influences on lobar and nonlobar ICH risks. Improved understanding of ICH risk associated with alcohol consumption among different race/ethnic groups may aid in focused counseling regarding alcohol use. Here, we explore the complex relationship

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between alcohol consumption and ICH in a large, multiethnic case-control prospective cohort of participants with ICH.

METHODS Standard protocol approvals, registrations, and patient consents. This study was approved by ethical

standards committee on human experimentation at each respective site, and written informed consent was obtained from all participants (or guardians of participants) participating in the study. This review follows the guidelines set forth by the Strengthening the Reporting of Observational Studies in Epidemiology statement.

Source sample and alcohol consumption. Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) study methods have been described previously.⁸ In brief, ERICH is a multicenter, prospective, case-control study, designed to recruit 1,000 non-Hispanic white patients, 1,000 non-Hispanic black patients, and 1,000 Hispanic patients with ICH, along with matched ICH-free controls, for the identification of genetic and epidemiologic risk factors for ICH and outcomes after ICH. Participants were recruited from 19 US sites comprising 42 hospitals. We identified controls through random digit dialing to match cases by age (± 5 years), sex, race/ethnicity, and geographic area. Inclusion into the study requires age >18 years; residency within 50 miles of the recruitment center (100 miles for population centers <1 million); white, black, or Hispanic race/ethnicity; and a spontaneous ICH, defined as the sudden onset of severe headache, altered level of consciousness, or focal neurologic deficit associated with a focal collection of blood within the brain parenchyma, seen on neuroimaging or at autopsy, and not attributable to hemorrhagic conversion of a cerebral infarction or other structural vascular anomalies. All participants or designated proxies underwent a standardized data collection protocol including a personal interview and medical chart abstraction. Comprehensive interviews on cases and controls included questions regarding alcohol consumption. Alcohol use within the last 3 months identified participants as users. A drink was defined as 12 ounces of beer, 4 ounces of wine, or 1.5 ounces of liquor. This was quantified for participants as a standard can of beer, glass of wine, shot of liquor, or mixed drink. Patterns of alcohol consumption were categorized, according to the same criteria as used in the Northern Manhattan Study to allow meaningful comparisons across studies, as none, rare (<1 drink per month), moderate (≥ 1 drink per month and ≤ 2 drinks per day), intermediate (>2 drinks per day and <5 drinks per day), and heavy (≥ 5 drinks per day).¹ Binge drinking was defined as the consumption of ≥ 6 drinks for men or ≥ 4 drinks for women on any one occasion.⁹ Frequency of binge drinking was categorized into never, less than monthly, monthly, weekly, and daily. Medical history questions included hypertension, diabetes mellitus (DM), hyperlipidemia, smoking, stimulant or narcotic use, coronary artery disease (CAD), myocardial infarction (MI), ischemic stroke, and atrial fibrillation. Highest level of education was categorized into those who did not graduate from high school, those who graduated from high school/technical school, and those with any post-high school education. Physical measurements obtained at presentation included body mass index (BMI) and systolic and diastolic blood pressures (BP), and laboratory data obtained include prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and random blood glucose. Neurologic outcomes at 3 months following hemorrhage were assessed by telephone using the modified Rankin Scale (mRS) score. Other data collected include location of hemorrhage, hemorrhage volume, and presence of microhemorrhages. BMI was also recorded for the control group.

Statistical analysis. Alcohol consumption was defined as none, rare, moderate, intermediate, or heavy. Two separate analysis designs were formulated. The first design, a 1:1 matched case/control design, compared baseline characteristics using a conditional

Table 1 Baseline demographics of controls and patients

	Controls (n = 2,660)	Patients (n = 2,660)	p Value
Age, y	62.3 $\pm$ 13.8	62.6 $\pm$ 14.0	Matched
Male	1,503 (56.5)	1,503 (56.5)	Matched
Race			Matched
Black	896 (33.7)	896 (33.7)	
White	961 (36.1)	961 (36.1)	
Hispanic	803 (30.2)	803 (30.2)	
BMI, kg/m ²	29.8 $\pm$ 6.8	28.9 $\pm$ 7.4	<0.0001
Hypertension (n = 2,628)	1,417 (53.9)	2,072 (78.8)	<0.0001
DM (n = 2,643)	568 (21.5)	679 (25.7)	0.0003
Hyperlipidemia (n = 2,521)	1,194 (47.4)	1,038 (41.2)	<0.0001
Smoking (n = 661)	196 (29.7)	254 (38.4)	0.0001
Cocaine/crack	5 (0.5)	88 (3.3)	<0.0001
Opiates	5 (0.2)	18 (0.7)	0.011
Marijuana	103 (3.9)	99 (3.7)	0.771
Amphetamine	6 (0.2)	23 (0.9)	0.003
Other substance abuse	1 (0.0)	7 (0.3)	0.069
CAD (n = 2,618)	222 (8.5)	325 (12.4)	<0.0001
MI (n = 2,646)	139 (5.3)	210 (7.9)	<0.0001
Ischemic stroke	32 (1.2)	253 (9.5)	<0.0001
Atrial fibrillation (n = 2,629)	140 (5.3)	238 (9.1)	<0.0001
Education (n = 2,630)			<0.0001
<High school	301 (11.4)	640 (24.3)	
High school	512 (19.5)	864 (32.9)	
Any college	1,817 (69.1)	1,126 (42.8)	
Alcohol use			<0.0001
None	1,116 (42.0)	1,429 (53.7)	
Rare	320 (12.0)	198 (7.4)	
Moderate	1,103 (37.7)	671 (25.2)	
Intermediate	120 (4.5)	109 (4.1)	
Heavy	101 (3.8)	253 (9.5)	
Any binge drinking (n = 2,658)	404 (15.2)	646 (24.3)	<0.0001
Binge drinking frequency (n = 2,595)			<0.0001
Never	2,211 (85.2)	2,004 (77.2)	
<Monthly	241 (9.3)	270 (10.4)	
Monthly	47 (1.8)	53 (2.0)	
Weekly	68 (2.6)	125 (4.8)	
Daily	28 (1.1)	143 (5.5)	

Abbreviations: BMI = body mass index; CAD = coronary artery disease; DM = diabetes mellitus; MI = myocardial infarction. Values are mean $\pm$ SD or n (%).

logistic regression. A multivariable analysis was performed using known risk factors. The second design used cases only; baseline characteristics between alcohol consumption levels were compared using χ^2 tests for categorical data and a one-way analysis of variance for continuous data. We performed multivariable analyses on continuous outcomes using generalized linear models and adjusted for known risk factors and any baseline differences. For both designs, odds ratios (ORs) were calculated for the 5 categories of alcohol use, and the no alcohol use category was the reference group. Analyses were performed on overall ICH and stratified by ICH location (lobar and nonlobar). Missing data was not imputed.

RESULTS Description of the study cohorts. At the time of analysis, data were available for 2,997 cases, enrolled between September 2010 and October 2015, of which 69 were excluded due to missing data for alcohol consumption. Of the remaining 2,931 cases, 2,660 were matched 1:1 to 2,660 ICH-free controls. Significantly higher proportions of cases had hypertension, DM, lower BMI, smoking history, cocaine/crack abuse, opiate abuse, amphetamine abuse, CAD, history of MI, history of ischemic stroke, and atrial fibrillation. A significantly lower proportion of cases reported hyperlipidemia history and education beyond high school compared to the controls. No differences were detected in marijuana abuse and any other substance abuse between the 2 groups. Characteristics of the 2 groups are presented in table 1.

Alcohol consumption and ICH risk. Significant differences in alcohol consumption were detected between the case and control groups. Cases were more likely to report no or heavy alcohol consumption, while the controls were more likely to report rare, moderate,

and intermediate alcohol consumption. Higher prevalence of binge drinking was detected in the case group, and patients in the case group also reported a higher frequency of binge drinking (table 1).

Multivariable analyses adjusting for baseline differences including hypertension, DM, hyperlipidemia, history of ischemic stroke, smoking, and marijuana and cocaine/crack abuse demonstrated protective effects of rare (OR 0.57 with 95% confidence interval [CI] [0.45–0.72], $p < 0.0001$) and moderate (OR 0.65 [0.55–0.77], $p < 0.0001$) alcohol consumption for ICH risk, relative to no alcohol consumption. Heavy alcohol consumption was associated with increased ICH risk (OR 1.77 [1.30–2.41], $p = 0.0003$), whereas intermediate alcohol consumption confers no increased ICH risk (OR 0.82 [0.58–1.16], $p = 0.27$). Subgroup analyses demonstrated protective effects of rare (OR 0.54 [0.35–0.83], $p = 0.005$) and moderate (OR 0.61 [0.45–0.82], $p = 0.001$) alcohol consumption for lobar ICH risk. Intermediate (OR 0.82 [0.44–1.52], $p = 0.52$) and heavy (OR 1.22 [0.71–2.10], $p = 0.48$) alcohol consumption did not demonstrate increased lobar ICH risk. Similarly, rare (OR 0.59 [0.44–0.79], $p = 0.0005$) and moderate (OR 0.67 [0.55–0.83], $p = 0.0002$) alcohol consumption was associated with decreased nonlobar ICH risk. In contrast to heavy alcohol consumption in lobar ICH risk, heavy alcohol consumption was associated with increased nonlobar ICH risk (OR 2.04 [1.39–3.01], $p = 0.0003$). The results of the multivariate analyses are presented in table 2.

Patterns of alcohol consumption. Younger age and male sex were associated with increased alcohol consumption. Those with different patterns of alcohol consumption demonstrated differences in race/ethnicity, hypertension, DM, hyperlipidemia, smoking, cocaine/crack abuse, opiate abuse, marijuana abuse, other substance abuse, CAD, MI, ischemic stroke, atrial fibrillation, highest level of education, binge drinking, binge drinking pattern, BMI, diastolic BP on presentation, initial PT, initial INR, initial total cholesterol, initial HDL, random blood glucose on presentation, and mRS score at 3 months. No differences in systolic BP on presentation, initial PTT, or initial LDL were found. In addition, no differences in hemorrhage location, hemorrhage volume, or presence of microhemorrhages on gradient echo sequences were detected among the different patterns of alcohol consumption. Case characteristics stratified by alcohol consumption pattern are presented in table 3.

Alcohol consumption and ICH risk in among the race/ethnic groups. Subgroup analyses by race/ethnic groups demonstrated decreased ICH risk for all

Table 2 Multivariate analyses of intracerebral hemorrhage (ICH) risk stratified by alcohol consumption pattern

Alcohol use	Odds ratio	95% Confidence interval	p Value
Rare	0.569	0.447–0.724	<0.0001
Moderate	0.649	0.548–0.767	<0.0001
Intermediate	0.822	0.581–1.162	0.267
Heavy	1.767	1.295–2.411	0.0003
Lobar ICH			
Rare	0.543	0.354–0.832	0.005
Moderate	0.608	0.452–0.819	0.001
Intermediate	0.815	0.439–1.516	0.519
Heavy	1.218	0.705–2.103	0.479
Nonlobar ICH			
Rare	0.591	0.44–0.794	0.0005
Moderate	0.671	0.546–0.826	0.0002
Intermediate	0.825	0.538–1.265	0.378
Heavy	2.044	1.388–3.009	0.0003

Adjustments were made for hypertension, diabetes mellitus, hypercholesterolemia, smoking, crack/cocaine abuse, marijuana abuse, ischemic stroke, and education level.

Table 3 Case cohort characteristics stratified by pattern of alcohol consumption

	None (n = 1,565)	Rare (n = 214)	Moderate (n = 739)	Intermediate (n = 121)	Heavy (n = 292)	p Value
Age, y	64.8 ± 14.8	61.9 ± 14.1	60.4 ± 14.5	57.8 ± 11.6	55.2 ± 10.1	<0.0001
Male	758 (48.4)	126 (58.9)	491 (66.4)	93 (76.9)	247 (84.6)	<0.0001
Race						0.0007
Black	526 (33.6)	58 (27.1)	232 (31.4)	42 (34.7)	110 (37.7)	
White	515 (32.9)	84 (39.3)	284 (38.4)	38 (31.4)	68 (23.3)	
Hispanic	524 (33.5)	72 (33.6)	223 (30.2)	41 (33.9)	114 (39.0)	
Hypertension	1,354 (86.8); 1,560	185 (86.4)	594 (80.5); 738	99 (82.5); 120	247 (84.9); 291	0.003
DM	526 (33.6); 1,564	68 (31.8)	180 (24.4)	20 (16.7); 120	57 (19.5)	<0.0001
Hyperlipidemia	796 (51.6); 1,542	103 (48.4); 213	309 (42.6); 726	46 (39.0); 118	81 (28.3); 286	<0.0001
Smoking	194 (29.0); 670	32 (30.5); 105	146 (39.5); 370	38 (49.4); 77	121 (66.1); 183	<0.0001
Cocaine/crack	23 (1.5)	3 (1.4)	37 (5.0)	11 (9.1)	25 (8.6)	<0.0001
Opiates	4 (0.3)	2 (0.9)	7 (0.9)	0 (0.0)	5 (1.7)	0.017
Marijuana	29 (1.9)	4 (1.9)	45 (6.1)	4 (3.3)	26 (8.9)	<0.0001
Amphetamine	11 (0.7)	4 (1.9)	6 (0.8)	1 (0.8)	3 (1.0)	0.418
Any other substance abuse	1 (0.1)	2 (0.9)	2 (0.3)	0 (0.0)	4 (1.4)	0.004
CAD	215 (13.9); 1,542	25 (11.7); 213	74 (10.2); 726	9 (7.4)	20 (6.9); 291	0.002
MI	146 (9.4); 1,558	15 (7.1); 211	46 (6.3); 735	2 (1.7)	15 (5.2); 291	0.002
Ischemic stroke	247 (15.8)	24 (11.2)	71 (9.6)	13 (10.7)	13 (4.5)	<0.0001
Atrial fibrillation	147 (9.5); 1,549	28 (13.1); 213	61 (8.3); 731	11 (9.1)	7 (2.4); 291	0.0003
Education						<0.0001
<High school	438 (28.3); 1,547	36 (16.9); 213	150 (20.5); 731	33 (27.7); 119	92 (31.6); 291	
High school	526 (34.0); 1,547	66 (31.0); 213	210 (28.7); 731	36 (30.3); 119	120 (41.2); 291	
Any college	583 (37.7); 1,547	111 (52.1); 213	371 (50.8); 731	50 (42.0); 119	79 (27.1); 291	
Binge drinking	173 (11.1); 1,564	29 (13.6)	219 (29.6)	71 (58.7)	237 (81.2)	<0.0001
Binge drinking frequency						<0.0001
Never	1,391 (90.3); 1,540	185 (87.3); 212	520 (72.3); 719	50 (42.7); 117	55 (19.5); 282	
<Monthly	99 (6.4); 1,540	21 (9.9); 212	124 (17.2); 719	26 (22.2); 117	19 (6.7); 282	
Monthly	8 (0.5); 1,540	3 (1.4); 212	22 (3.1); 719	8 (6.8); 117	18 (6.4); 282	
Weekly	17 (1.1); 1,540	2 (0.9); 212	44 (6.1); 719	27 (23.1); 117	60 (21.3); 282	
Daily	25 (1.6); 1,540	1 (0.5); 212	9 (1.3); 719	6 (5.1); 117	130 (46.1); 282	
BMI, kg/m ²	28.9 ± 7.4; 1,517	30.9 ± 9.0; 213	28.7 ± 7.0; 715	28.6 ± 7.4; 116	28.1 ± 6.3; 286	0.0004
Systolic BP, mm Hg	183.6 ± 37.9; 1,393	188.0 ± 36.0; 192	186.9 ± 38.0; 668	191.3 ± 35.9; 111	187.4 ± 36.5; 267	0.076
Diastolic BP, mm Hg	99.6 ± 25.0; 1,393	104.4 ± 24.2; 192	104.4 ± 25.6; 668	110.6 ± 23.9; 111	107.2 ± 24.1; 267	<0.0001
mRS score at 3 mo						0.009
0	55 (4.0); 1,360	13 (7.1); 184	29 (4.7); 662	8 (8.5); 94	9 (3.6); 250	
1	191 (14.0); 1,360	28 (15.2); 184	120 (19.3); 662	20 (21.3); 94	39 (15.6); 250	
2	195 (14.3); 1,360	31 (16.8); 184	118 (19.0); 662	16 (17.0); 94	48 (19.2); 250	
3	209 (15.4); 1,360	22 (12.0); 184	97 (15.6); 662	13 (13.8); 94	36 (14.4); 250	
4	265 (19.5); 1,360	35 (19.0); 184	108 (17.4); 662	16 (17.0); 94	45 (18.0); 250	
5	116 (8.5); 1,360	19 (10.3); 184	45 (7.2); 662	3 (3.2); 94	16 (6.4); 250	
6	329 (24.2); 1,360	36 (19.6); 184	105 (16.9); 662	18 (19.1); 94	57 (22.8); 250	
PT	14.9 ± 10.8; 1,468	14.0 ± 6.0; 205	13.6 ± 5.7; 690	13.6 ± 4.3; 112	13.2 ± 3.5; 282	0.003
PTT	30.0 ± 9.2; 1,340	29.3 ± 11.1; 195	28.8 ± 6.9; 641	29.1 ± 6.3; 103	29.4 ± 5.7; 260	0.060
INR	1.3 ± 0.9; 1,506	1.2 ± 0.6; 212	1.1 ± 0.5; 711	1.2 ± 0.5; 117	1.2 ± 0.7; 288	0.002
Total cholesterol, mg/dL	170.6 ± 44.8; 923	179.9 ± 48.1; 127	179.3 ± 45.5; 427	179.0 ± 40.2; 70	177.6 ± 49.2; 181	0.006

Continued

Table 3 Continued

	None (n = 1,565)	Rare (n = 214)	Moderate (n = 739)	Intermediate (n = 121)	Heavy (n = 292)	p Value
LDL, mg/dL	101.0 ± 39.0; 906	110.3 ± 40.1; 123	101.7 ± 36.5; 409	104.6 ± 35.7; 69	98.3 ± 41.6; 175	0.087
HDL, mg/dL	47.5 ± 17.0; 915	45.6 ± 14.2; 126	52.1 ± 20.6; 420	50.4 ± 17.9; 69	55.9 ± 23.9; 176	<0.0001
Random glucose, mg/dL	153.6 ± 67.7; 1,518	155.3 ± 72.0; 210	145.9 ± 62.8; 710	141.7 ± 48.9; 117	141.9 ± 58.3; 283	0.004
Location						0.065
Brainstem	73 (4.8); 1,535	13 (6.2); 209	41 (5.7); 725	8 (6.9); 116	18 (6.4); 282	
Cerebellum	132 (8.6); 1,535	13 (6.2); 209	52 (7.2); 725	9 (7.8); 116	19 (6.7); 282	
Nonlobar	780 (50.8); 1,535	119 (56.9); 209	405 (55.9); 725	65 (56.0); 116	173 (61.3); 282	
Lobar	523 (34.1); 1,535	63 (30.1); 209	213 (29.4); 725	33 (28.4); 116	66 (23.4); 282	
Intraventricular	27 (1.8); 1,535	1 (0.5); 209	14 (1.9); 725	1 (0.9); 116	6 (2.1); 282	
ICH volume, mL ³	20.3 ± 25.9; 1,514	19.5 ± 23.1; 207	19.2 ± 22.9; 720	23.3 ± 31.8; 115	22.9 ± 26.2; 280	0.184
Microhemorrhages	264 (54.9); 481	38 (53.5); 71	125 (48.8); 256	26 (65.0); 40	44 (45.8); 96	0.151

Abbreviations: BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; DM = diabetes mellitus; HDL = high-density lipoprotein; ICH = intracerebral hemorrhage; INR = international normalized ratio; LDL = low-density lipoprotein; MI = myocardial infarction; mRS = modified Rankin Scale; PT = prothrombin time; PTT = partial thromboplastin time.

Values are mean ± SD; total N or n (%); total N.

categories of alcohol consumption for white participants. For black participants, rare alcohol consumption was associated with decreased ICH risk (OR 0.52 [0.33–0.80], $p = 0.003$), while both moderate (OR 0.74 [0.54–1.01], $p = 0.06$) and intermediate (OR 1.37 [0.74–2.54], $p = 0.31$) alcohol consumption demonstrated no increased risk. Heavy alcohol consumption was associated with increased ICH risk (OR 2.41 [1.36–4.27], $p = 0.003$). In the Hispanic population, heavy alcohol consumption was associated with significant ICH risk (OR 8.47 [3.76–19.08], $p < 0.0001$), while rare, moderate, and intermediate alcohol consumption demonstrated no increased ICH risk.

Further stratification into lobar and nonlobar ICH groups demonstrated decreased lobar ICH risk among white patients with rare (OR 0.55 [0.31–0.98], $p = 0.043$) and moderate (OR 0.52 [0.34–0.78], $p = 0.002$) alcohol consumption. Rare (OR 0.45 [0.26–0.76], $p = 0.003$), moderate (OR 0.45 [0.31–0.65], $p < 0.0001$), and intermediate (OR 0.41 [0.20–0.85], $p = 0.017$) alcohol consumption in white patients was associated with decreased nonlobar ICH. In the black population, rare (OR 0.18 [0.06–0.55], $p = 0.003$) alcohol consumption was associated with decreased lobar ICH risk. Heavy (OR 2.34 [1.19–4.61], $p = 0.014$) alcohol consumption in black patients was associated with increased nonlobar ICH risk. Alcohol consumption was not associated with increased lobar ICH risk in the Hispanic population. Heavy (OR 12.32 [5.05–46.45], $p < 0.0001$) alcohol consumption was associated with significant nonlobar ICH risk in the Hispanic population. The results of the multivariate analyses stratified by race/ethnic groups are presented

in table 4. Further analysis showed a significant interaction between race/ethnicity and alcohol use on ICH risk ($p < 0.0001$). No significant interaction was found between race/ethnicity and binge drinking on ICH risk ($p = 0.49$).

DISCUSSION Despite progress in the understanding and management of ischemic stroke, the pathophysiology of ICH remains poorly understood, and its associated morbidity and mortality remains dismal.^{10,11} Due to the limited treatment regimens currently available for ICH, approaches to the disease process have focused on prevention. Major risk factors identified for ICH in the literature include male sex, age, hypertension, and alcohol consumption.⁵ The 2 modifiable risk factors, hypertension and alcohol consumption, have an intricate and complex relationship. Moderate alcohol consumption independently demonstrates protective effects in CAD and ischemic stroke.^{1,2,12–14} The relationship between alcohol consumption and ICH remains unclear; studies have demonstrated increased ICH risk with heavy alcohol consumption; however, heterogeneous cohorts and small sample size in these studies have limited analysis of dose-dependent relationship between alcohol intake and ICH risk.^{3–5,7,15–18}

The findings from our study demonstrated the association of rare (<1 drink per month) and moderate (≥ 1 drink per month and ≤ 2 drinks per day) alcohol consumption with decreased ICH risk. Heavy (≥ 5 drinks per day) alcohol consumption was associated with increased ICH, while intermediate (> 2 drinks per day and < 5 drinks per day) alcohol consumption demonstrated no associated

Table 4 Multivariate analyses of intracerebral hemorrhage (ICH) risk stratified by alcohol consumption pattern for different race/ethnic groups

Alcohol use	Odds ratio	95% Confidence interval	p Value
White			
Rare	0.491	0.334–0.723	0.0003
Moderate	0.488	0.374–0.637	<0.0001
Intermediate	0.488	0.287–0.831	0.008
Heavy	0.605	0.374–0.979	0.041
Lobar ICH			
Rare	0.551	0.308–0.984	0.044
Moderate	0.518	0.344–0.781	0.002
Intermediate	0.617	0.278–1.368	0.234
Heavy	0.671	0.317–1.419	0.296
Nonlobar ICH			
Rare	0.446	0.264–0.755	0.003
Moderate	0.452	0.313–0.652	<0.0001
Intermediate	0.409	0.196–0.853	0.017
Heavy	0.532	0.278–1.018	0.057
Black			
Rare	0.516	0.332–0.803	0.003
Moderate	0.741	0.542–1.013	0.060
Intermediate	1.372	0.743–2.535	0.312
Heavy	2.410	1.360–4.269	0.003
Lobar ICH			
Rare	0.181	0.060–0.547	0.003
Moderate	0.815	0.420–1.581	0.545
Intermediate	1.111	0.247–5.003	0.891
Heavy	2.349	0.711–7.760	0.161
Nonlobar ICH			
Rare	0.645	0.391–1.063	0.085
Moderate	0.702	0.485–1.016	0.060
Intermediate	1.545	0.757–3.152	0.232
Heavy	2.341	1.188–4.613	0.014
Hispanic			
Rare	0.695	0.437–1.105	0.124
Moderate	0.804	0.579–1.115	0.191
Intermediate	0.936	0.426–2.053	0.868
Heavy	8.474	3.764–19.082	<0.0001
Lobar ICH			
Rare	1.140	0.444–2.929	0.786
Moderate	0.550	0.279–1.087	0.085
Intermediate	1.330	0.238–7.430	0.745
Heavy	3.020	0.733–12.440	0.126
Nonlobar ICH			
Rare	0.583	0.335–1.016	0.057
Moderate	0.923	0.627–1.358	0.684

Continued

risk. A meta-analysis on the association of alcohol consumption and relative risk (RR) of stroke demonstrated a linear relationship between alcohol consumption and hemorrhagic stroke among 12 studies, and no protective effects were seen with alcohol consumptions of <12 g/d (RR 0.79 [0.60–1.05]) or 12–24 g/d (RR 0.98 [0.77–1.25]).¹⁹ A more recent meta-analysis found that any dose of alcohol was associated with increased risk of hemorrhagic stroke, except in women who consume less than 36 g or 3 drinks a day (RR 0.69 [0.54–0.89]).²⁰ However, it must be noted that not all studies included in these meta-analyses differentiate spontaneous ICH from other types of hemorrhagic stroke (i.e., subarachnoid hemorrhage) or causes of hemorrhage (i.e., arteriovenous malformation, aneurysm), which may explain some of the discordant findings.

Despite our finding of lower ICH risk with moderate alcohol consumption, it must be noted that increased alcohol consumption is associated with younger age at ICH diagnosis. Subgroup analyses from the current study demonstrated association of rare and moderate alcohol consumption with decreased lobar and nonlobar ICH risks. While heavy alcohol consumption was associated with increased nonlobar ICH risk, it was not associated with increased lobar ICH risk. Analysis of race/ethnic groups demonstrated decreased ICH risk with alcohol consumption in the white population. Rare and moderate alcohol consumption was associated with decreased lobar ICH risk, and rare, moderate, and intermediate consumption was associated with decreased nonlobar ICH risk in the white population. In the black population, rare alcohol consumption was associated with decreased ICH risk, while heavy alcohol consumption was associated with increased ICH risk. Rare alcohol consumption was associated with decreased lobar ICH risk, and heavy alcohol consumption was associated with increased nonlobar ICH risk in black participants. Heavy alcohol consumption in Hispanic participants demonstrated significant ICH risk with OR of approximately 8.5. Alcohol consumption was not associated with lobar ICH risk; however, heavy alcohol consumption in Hispanic participants demonstrated significant nonlobar ICH risk with OR of approximately 12.3.

The protective relationship between alcohol consumption and CAD has been reiterated in several studies.^{21,22} This protective effect appears to be derived from an increased HDL concentration with alcohol consumption. Although increased HDL may have protective effects on ischemic stroke risk, it actually confers increased ICH risk.⁴ In contrast, increased concentration of non-HDL cholesterol has been associated with reduced risk of ICH; its

Table 4 Continued

Alcohol use	Odds ratio	95% Confidence interval	p Value
Intermediate	0.754	0.303–1.876	0.544
Heavy	12.315	5.049–46.454	<0.0001

Adjustments were made for hypertension, diabetes mellitus, hypercholesterolemia, smoking, crack/cocaine abuse, marijuana abuse, ischemic stroke, and education level.

mechanism remains unclear, but has been hypothesized to play a pathophysiologic role in the maintenance of vascular integrity.^{4,23,24} Hypertension is also an important risk for ICH, and alcohol consumption has been associated with hypertension.^{4,5,23} However, the development of hypertension appears to be associated with intermediate or heavy alcohol consumption.¹³ In a population study involving 83,947 ambulatory adult participants, significant increases in BP were detected in those who consumed more than 2 drinks per day.²⁵ This relationship was reconfirmed in an updated study by the same authors with 66,510 patients.²⁶ Therefore, when consumed in rare or moderate amounts, alcohol may confer protective effects on ICH risk via mechanisms independent of HDL and at the same time avoids the risk of hypertension. It remains unclear what that mechanism is, as the benefit of rare and moderate alcohol consumption persists after adjusting for hypertension and hyperlipidemia among other factors. Genetic and metabolic differences between races/ethnic groups seem to play a significant role in the effects of alcohol consumption and subsequent ICH risk as demonstrated in this study. The key enzymes involved in alcohol metabolism are alcohol dehydrogenase and aldehyde dehydrogenase.²⁷ Several variants of these enzymes exist that differ in their ability to break down alcohol and its toxic metabolite acetaldehyde, and these variants may account for ethnic/racial differences in alcohol-associated hypertension, tolerance, cancer risk, and pancreatitis.^{28–32} Other pathways of alcohol metabolism include the microsomal ethanol oxidizing system, catalase within the peroxisomes, and nonoxidative pathways.^{33–36} Despite the extensive work on characterizing the enzymatic variants of the alcohol metabolism pathways, a potential association between racial/ethnic variations in alcohol metabolism and ICH risk has yet to be investigated.

There are potential limitations to this study. First, the results of the study are contingent upon the accuracy of alcohol history reporting, and family members may be relied upon for patients who were not able to provide detailed history. Thus this study may suffer from reporting and recall biases. Second, the stratification of alcohol consumption was based on the number of drinks, and data regarding the exact amount of alcohol consumed were not available.

No distinction was made between former drinkers and lifelong abstainers; however, the “sick quitters” hypothesis remains controversial, as demonstrated by the results of previous large cohort studies on the effects of alcohol on cardiovascular diseases.^{37–40} Future work should aim to delineate the threshold of the beneficial effects of alcohol using more specific alcohol content within drinks. In addition, further understanding of the mechanism by which alcohol confers its protective effects is needed. The strengths of this study must also be noted. This is the largest study to date in the literature investigating alcohol consumption and ICH risk. This study recruited a multiethnic population with ICH that was specifically designed to have equal power among minority populations, while prior studies in the literature may have been limited by power.

The findings of the ERICH study demonstrated the association of rare and moderate alcohol consumption with decreased ICH risk in a multiracial/ethnic population, in contrast to the majority of current literature. Heavy alcohol consumption was associated with increased ICH risk. Race/ethnicity was a significant factor in alcohol-associated ICH risk; heavy alcohol consumption in black and Hispanic people poses significant nonlobar ICH risk. The mechanism by which alcohol confers these potential protective effects remains to be determined. The results of this study support the previous recommendations on the moderate consumption of alcohol in cardiovascular disease prevention for the general population.

AUTHOR CONTRIBUTIONS

Ching-Jen Chen: drafting of manuscript, data interpretation, critical revision of the manuscript for important intellectual content. W. Mark Brown: data analysis and interpretation, critical revision of the manuscript for important intellectual content. Charles J. Moomaw: acquisition of data, data analysis and interpretation, critical revision of the manuscript for important intellectual content. Carl D. Langefeld: data analysis and interpretation, critical revision of the manuscript for important intellectual content. Jennifer Osborne: acquisition of data, critical revision of the manuscript for important intellectual content. Bradford B. Worrall: data interpretation, critical revision of the manuscript for important intellectual content. Daniel Woo: data interpretation, critical revision of the manuscript for important intellectual content, study supervision. Sebastian Koch: data interpretation, critical revision of the manuscript for important intellectual content, study supervision.

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