ARTICLE

Alcohol intake and the risk of intracerebral hemorrhage in the elderly

The MUCH-Italy

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Abstract

Objective

To investigate the role of alcohol as a causal factor for intracerebral hemorrhage (ICH) and whether its effects might vary according to the pathogenic mechanisms underlying cerebral bleeding.

Methods

We performed a case-control analysis, comparing a cohort of consecutive white patients with ICH aged 55 years and older with a group of age- and sex-matched stroke-free controls, enrolled in the setting of the Multicenter Study on Cerebral Haemorrhage in Italy (MUCH-Italy) between 2002 and 2014. Participants were dichotomized into excessive drinkers (>45 g of alcohol) and light to moderate drinkers or nondrinkers. To isolate the unconfounded effect of alcohol on ICH, we used causal directed acyclic graphs and the back-door criterion to select a minimal sufficient adjustment set(s) of variables for multivariable analyses. Analyses were performed on the whole group as well as separately for lobar and deep ICH.

Results

We analyzed 3,173 patients (1,471 lobar ICH and 1,702 deep ICH) and 3,155 controls. After adjusting for the preselected variables in the minimal sufficient adjustments, heavy alcohol intake was associated with deep ICH risk (odds ratio [OR], 1.68; 95% confidence interval [CI], 1.36–2.09) as well as with the overall risk of ICH (OR, 1.38; 95% CI, 1.17–1.63), whereas no effect was found for lobar ICH (OR, 1.01; 95% CI, 0.77–1.32).

Conclusions

In white people aged 55 years and older, high alcohol intake might exert a causal effect on ICH, with a prominent role in the vascular pathologies underlying deep ICH.

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Glossary

BMI = body mass index; **CI** = confidence interval; **DAG** = directed acyclic graph; **ERICH** = Ethnic/Racial Variations of Intracerebral Hemorrhage; **ICH** = intracerebral hemorrhage; **MSA** = minimal sufficient adjustment; **MUCH-Italy** = Multicenter Study on Cerebral Haemorrhage in Italy; **OR** = odds ratio; **SEM** = structural equation model.

Although the relationship between alcohol consumption and intracerebral hemorrhage (ICH) has been a matter of long debate and numerous epidemiologic analyses, the available data are far from conclusive.[1,2] In view of the potential clinical and public health significance of this relation, we aimed at estimating any effect of alcohol intake on cerebral bleeding in a case-control study comprising one of the largest collections of patients with ICH reported to date.

Methods

Study group and design

The Multicenter Study on Cerebral Haemorrhage in Italy (MUCH-Italy) is a countrywide network of neurologic centers designed to investigate epidemiology, risk factors, and consequences of ICH in the setting of a multicenter, hospital-based, prospectively recruiting, observational study.[3,4] The MUCH-Italy is coordinated by the University of Brescia, Italy. It also consists of a biostatistical core (University of Pavia) and 19 Italian clinical recruiting centers. For the present analysis, we screened datasets from patients with acute ICH admitted consecutively from January 1, 2002, to July 31, 2014.

Standard protocol approvals, registrations, and patient consents

The institutional review board at each participating study center provided approval for the study. Written informed consent was obtained for all participants (or next of kin).

Cases

Eligibility for study participation required neuroimaging (CT or MRI) confirmation of hemorrhagic stroke. Exclusion criteria included the presence of trauma, brain tumor, or hemorrhagic transformation of a cerebral infarction, vascular malformation, or any other perceived cause of secondary ICH. Hematoma location was assigned based on admission CT scan by stroke neurologists at each participating center. ICHs isolated to the cortex (with or without involvement of subcortical white matter) were defined as *lobar ICH*, while ICHs selectively involving the thalamus, basal ganglia, or brainstem were defined as *deep* (*nonlobar*) *ICH*. Cerebellar hematomas were included in the subgroup of patients with lobar ICH, based on the observation that pathologically proven cerebral amyloid angiopathy was detected in half of these cases.[5] Multiple concurrent bleeds involving deep and lobar territories were defined as mixed ICH and represented an exclusion criterion.

Controls

Controls were recruited from the Moli-Sani project, an Italian population-based study recruiting citizens of the Molise region, aimed at investigating the equilibrium between genetics and environment in the pathogenesis of cardiovascular, cerebrovascular, and cancer disease.[6] Individuals included were matched with cases by sex and age (±3 years) and were confirmed to have no medical history of stroke through interview and review of medical records.

Definitions of risk factors

A history of vascular risk factors was defined by the presence of predisposing conditions, either in the personal medical history for both cases and controls or identified during admission for ICH cases. Hypertension was defined as systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg out of the acute phase, or current pharmacologic treatment for hypertension. Diabetes was defined as fasting glucose levels >6.9 mmol/L out of the acute phase or current treatment with antidiabetic drugs. Hypercholesterolemia was defined as total serum cholesterol levels >6.2 mmol/L out of the acute phase or using pharmacologic treatment to lower blood lipids. Smoking was defined as currently smoking one or more cigarettes per day on a regular basis. We collected information on atrial fibrillation (medical history or ECG findings at admission), coronary artery disease (medical history of angina, myocardial infarction, coronary artery bypass graft, or percutaneous transluminal coronary angioplasty), and history of stroke or TIA (based on clinical history). Finally, we collected data about pre-ICH medications (warfarin, aspirin, or other antiplatelet agents, antihypertensive agents, oral hypoglycemic agents or insulin, and statins). For the purpose of the present analysis, we selected only patients aged 55 years or older. Information on drinking habit was collected by physicians in each center by direct interview with patients or relatives/caregivers. In calculating the amount of alcohol consumed (in grams per day), it was assumed that 120 mL of wine, 330 mL of beer, or 40 mL of liquor contains 12 g of ethanol. Thus, 12 g/d of ethanol is equivalent to 1 alcoholic beverage. Heavy alcohol intake during the year before enrollment was defined as a regular consumption of more than 300 g alcohol/wk (i.e., more than 45 g alcohol/d). Such a cutoff value was selected a priori without reference to the data. Participants were dichotomized, based on daily alcohol consumption, into excessive drinkers (>45 g of alcohol) and light to moderate drinkers or nondrinkers (≤45 g of alcohol).

Statistical analysis

We compared the characteristics of patients with ICH and controls using the χ^2 test for categorical variables and the *t* test for continuous variables. We used directed acyclic graphs (DAGs) and Pearl back-door criterion to select a minimal sufficient adjustment (MSA) set(s) of variables that should be

adjusted for in a multivariable analysis in order to isolate an unconfounded effect of alcohol on ICH.[7,8] In particular, we applied the following workflow.

DAG identification

We selected those factors derived from the MUCH-Italy database affecting alcohol consumption or ICH (i.e., age, sex, body mass index [BMI], smoking habit, hypertension, hypercholesterolemia, diabetes, and antithrombotic medications). Age was a numeric variable, while the other variables were binary. Because of the low frequency of oral anticoagulant medication users among controls, we deleted the variable oral anticoagulant medications from the list of covariates. Based on this selection, we computed a heterogeneous correlation matrix of polychoric (binary-binary variables) and polyserial (numeric-binary variables) correlations, and searched the skeleton (the undirected graph) of the suggestive conditional pairwise associations ($p < 0.05$) with the *skeleton*( ) function of the *pcalg* package.[9] The output graph is displayed in figure 1A. Then, we defined a priori, based on our guess and previous literature evidence, the direction of the links in the skeleton. We forced the non–statistically significant links age → hypercholesterolemia and age → hypertension. The proposed DAG is summarized in figure 1B.

Evaluation of DAG consistency

We evaluated whether the DAG restrictions generated from the "directed-separation" (d-separation) rule[7] encoded in the identified directions are correct (true). Briefly, the set of conditional independence assumptions (the missing links) encoded in the DAG as "X is independent of Y given Z" are the null hypotheses [H0: link(X–Y|Z) = 0]. These were statistically tested with the *localTests*( ) function of the *dagitty* package,[10] using the heterogeneous correlation matrix. The results are reported in table 1.

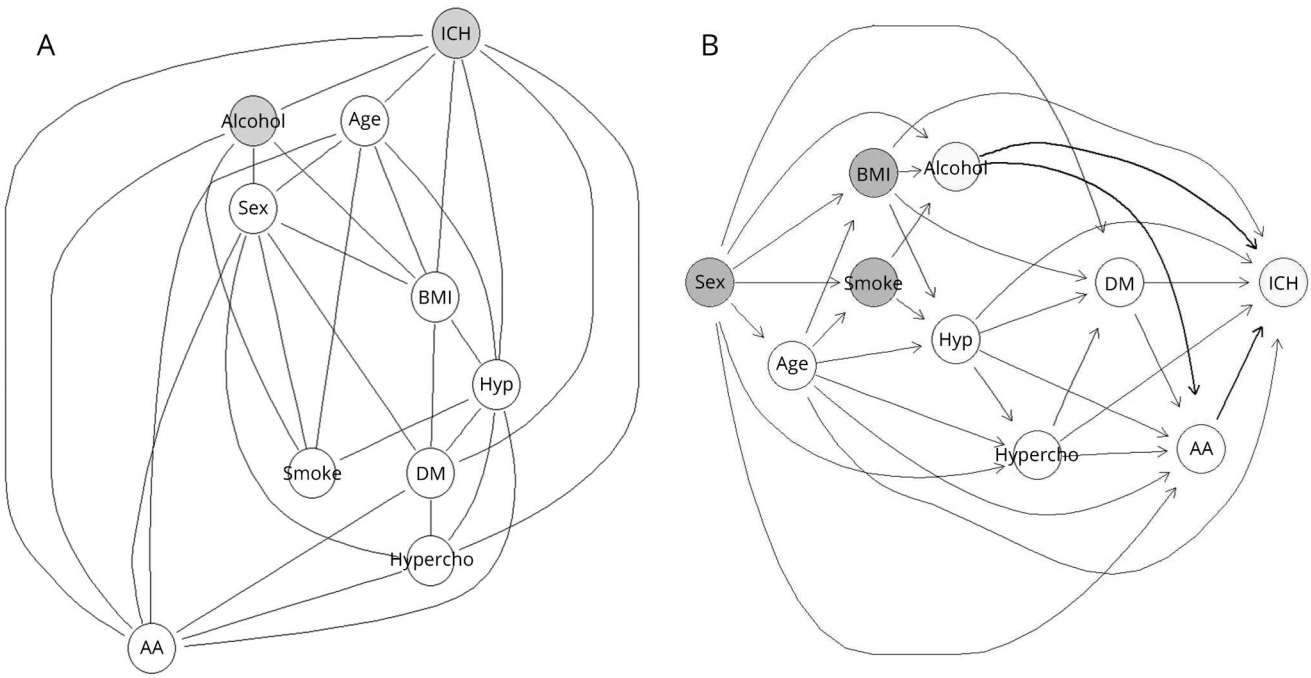
Only a p value (the missing link BMI-AA, for both the tests) was statistically significant after Bonferroni correction: $\alpha = 0.05/19 = 0.002632$. Vice versa, the encoded direct links in the DAG were all statistically significant [H0: link(X–Y) = 0 was rejected] based on a structural equation model (SEM) analysis of binary variables with bootstrap (B = 1,000 samples) testing, using the *sem*( ) function of the *lavaan* package[11] (table 2).

Similar results for DAG restrictions and DAG consistency were obtained with the *sem.missing.paths*( ) function and *sem.coefs*( ) function of the *piecewiseSEM* package,[12] using the original dataset and logistic models with default Wald testing, respectively (data not shown).

MSA set(s)

The MSA set(s) is obtained by heuristic search of the confounding paths for the X–Y relationships. A back-door path from X = exposure to Y = outcome is: "a path which (1) starts from X and ends at Y, and (2) has an arrow pointing into X."[8]

Figure 1 Skeleton (the undirected graph) of the observed variables obtained using the PC algorithm (A), and directed acyclic graph (B) for the unconfounded effect of heavy alcohol consumption on ICH



An edge between i and j, i–j is present if and only if variables i and j are conditionally dependent ($p < 0.05$) given a set S of all possible subsets S of the remaining variables. AA = antiplatelet agents; BMI = body mass index; DM = diabetes mellitus; Hyp = hypertension; Hypercho = hypercholesterolemia; ICH = intracerebral hemorrhage.

Table 1 Direct acyclic graph consistency evaluation testing conditional independence assumptions (missing links)

	Conditional independence	Estimate	SE	*p* Value
1	ICH _||_ smoke | age, alcohol, BMI, hypertension, sex	0.019245	0.013736	0.161217
2	Antiplatelet agents _||_ BMI | age, alcohol, diabetes, hypertension, hypercholesterolemia, sex	−0.05239	0.013692	0.000135
3	Antiplatelet agents _||_ smoke | age, alcohol, BMI, hypertension, sex	−0.01593	0.013731	0.246238
4	Antiplatelet agents _||_ smoke | age, alcohol, diabetes, hypertension, hypercholesterolemia, sex	−0.00993	0.013736	0.469946
5	Age _||_ alcohol | BMI, sex, smoke	−0.01863	0.013727	0.175003
6	Age _||_ diabetes | BMI, hypertension, hypercholesterolemia, sex	0.026508	0.013732	0.053601
7	Alcohol _||_ diabetes | BMI, hypertension, hypercholesterolemia, sex	−0.0309	0.013718	0.024463
8	Alcohol _||_ diabetes | age, BMI, hypertension, sex	−0.03098	0.013717	0.024098
9	Alcohol _||_ diabetes | BMI, sex, smoke	−0.03071	0.013716	0.025345
10	Alcohol _||_ hypertension | age, BMI, smoke	−0.00573	0.013734	0.676793
11	Alcohol _||_ hypertension | BMI, sex, smoke	−0.00525	0.013734	0.702058
12	Alcohol _||_ hypercholesterolemia | age, hypertension, sex	−0.0104	0.013732	0.449158
13	Alcohol _||_ hypercholesterolemia | BMI, sex, smoke	−0.00887	0.013732	0.518271
14	BMI _||_ hypercholesterolemia | age, hypertension, sex	0.00363	0.013736	0.791565
15	BMI _||_ smoke | age, sex	−0.02453	0.013721	0.074096
16	Diabetes _||_ smoke | age, BMI, hypertension, sex	−0.01617	0.01373	0.239081
17	Diabetes _||_ smoke | BMI, hypertension, hypercholesterolemia, sex	−0.01805	0.013729	0.188779
18	Hypertension _||_ sex | age, BMI, smoke	0.018372	0.013734	0.181016
19	Hypercholesterolemia _||_ smoke | age, hypertension, sex	−0.02479	0.013722	0.071083

Abbreviations: BMI = body mass index; ICH = intracerebral hemorrhage.
X_||_Y | Z means X and Y are conditionally independent given Z.

Confounding paths are defined with "unblocked" or "open" back-door paths, and the confounders of the X–Y relationship are the variables on the back-door paths. Various algorithms are implemented for identifying confounding path and confounders. We performed a search algorithm by a generalized version of the Pearl back-door criterion[13] to identify an MSA set(s) of variables that should be adjusted for in a multivariable analysis in order to isolate an unconfounded effect of X = alcohol on Y = ICH. An important DAG limitation is that different DAGs can have exactly the same testable implications. Therefore, we used the *equivalentDAGs*( ) function of the *dagitty* package to generate a list of all possible DAGs (i.e., the so-called "equivalence class" of DAGs) that are statistically equivalent to the a priori–identified and data-evaluated DAG. If the same Z = MSA set(s) applies to X = alcohol on Y = ICH in all of the DAGs in an equivalent class, then this greatly supports the validity that this (these) set(s) intercepts all the confounding paths between X = alcohol and Y = ICH. In this way, the causal effect of X on Y is identified by conditioning on Z. Ten equivalent classes (ec = 10) were derived by the search algorithm (figure 2), and only 5 links can be reversed (reverse = 5) without changing the equivalence class.

The output of the *adjustmentSets*( ) function of the *dagitty* package indicated that 2 MSA sets ([age, bmi, hyp, sex] and [bmi, sex, smoke]) remained valid for the entire equivalence class of DAGs for the X = alcohol on Y = ICH link under investigation. Thus, for our DAG, the statistical equivalence of DAGs is not an issue for the validity of the adjustment set(s) determined.

Logistic regression

Logistic regression was fitted to estimate the unconfounded causal effect (i.e., adjusted for the minimal sufficient [age, bmi, hyp, sex] or [bmi, sex, smoke] sets) of alcohol consumption on ICH, as well as on deep ICH and lobar ICH subtypes, respectively. The logistic regression parameter estimates were re-expressed as odds ratios (ORs) and 95% confidence intervals (CIs). The threshold for statistical significance was set at $p < 0.05$ for all analyses. Data were analyzed using SPSS for Windows version 21.0 (IBM Corp., Armonk, NY) and R version 3.4.3 packages (cran.r-project.org).

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Table 2 Direct acyclic graph consistency evaluation testing the encoded direct links based on a structural equation model analysis of binary variables with *z* test (estimate/SE), using bootstrap (B = 1,000 samples) SEs

	Estimate	SE	*z* Value	*p* Value
Regressions				
ICH				
Sex	0.031	0.013	2.289	0.022
Age	0.049	0.008	6.1	0
Alcohol	0.087	0.019	4.567	0
BMI	−0.16	0.014	−11.493	0
Hypertension	0.14	0.014	9.942	0
Hypercholesterolemia	−0.084	0.015	−5.7	0
Diabetes	0.094	0.019	5.063	0
Antiplatelet agents	0.199	0.016	12.366	0
Alcohol				
Sex	−0.125	0.009	−13.331	0
Smoke	0.075	0.019	3.983	0
BMI	0.057	0.011	5.243	0
Hypercholesterolemia				
Age	−0.025	0.007	−3.681	0
Sex	0.053	0.013	4.081	0
Hypertension	0.134	0.013	10.724	0
BMI				
Sex	0.065	0.013	4.953	0
Age	−0.045	0.007	−6.432	0
Smoke				
Sex	−0.058	0.008	−7.245	0
Age	−0.06	0.005	−11.542	0
Diabetes				
Sex	−0.07	0.01	−7.094	0
BMI	0.069	0.012	5.955	0
Hypercholesterolemia	0.069	0.012	5.847	0
Hypertension	0.058	0.01	5.751	0
Hypertension				
Age	0.085	0.008	11.301	0
BMI	0.081	0.014	5.922	0
Smoke	−0.083	0.022	−3.747	0
Antiplatelet agents				
Age	0.085	0.007	12.529	0
Sex	−0.08	0.012	−6.838	0
Alcohol	−0.057	0.015	−3.825	0

Continued

Table 2 Direct acyclic graph consistency evaluation testing the encoded direct links based on a structural equation model analysis of binary variables with *z* test (estimate/SE), using bootstrap (B = 1,000 samples) SEs *(continued)*

	Estimate	SE	*z* Value	*p* Value
Hypercholesterolemia	0.147	0.014	10.715	0
Hypertension	0.133	0.011	12.212	0
Diabetes	0.081	0.017	4.844	0
Age				
Sex	0.271	0.022	12.181	0
Variances				
ICH	0.216	0.002	98.698	0
Alcohol	0.116	0.003	35.914	0
Hypercholesterolemia	0.199	0.003	76.558	0
BMI	0.207	0.003	80.23	0
Smoke	0.091	0.003	28.468	0
Diabetes	0.127	0.003	38.767	0
Hypertension	0.217	0.002	99.988	0
Antiplatelet agents	0.161	0.003	56.245	0
Age	0.699	0.014	50.145	0

Abbreviations: BMI = body mass index; ICH = intracerebral hemorrhage.

Results

The current study targets 3,173 patients enrolled in the MUCH-Italy registry and 3,155 controls. As expected, patients with ICH were more likely to have an unfavorable cardiovascular risk factor profile, including hypertension and diabetes mellitus, were more frequently under treatment with antithrombotic medications (antiplatelet agents and oral anticoagulants) but were less frequently hypercholesterolemic in comparison with controls. A personal history of heavy alcohol consumption was more common in the subgroup of patients with deep ICH as compared to the corresponding subgroup of controls (16.6% vs 11.6%, p = 0.016), while it did not differ from that in the corresponding control group in the whole group of cases (14.2% vs 13.2%, p = 0.232) as well as in the subgroup of patients with lobar ICH (11.3% vs 12.6%, p = 0.287). Demographic characteristics of the study population, grouped according to hematoma location and prevalence of selected risk factors, are presented in table 3.

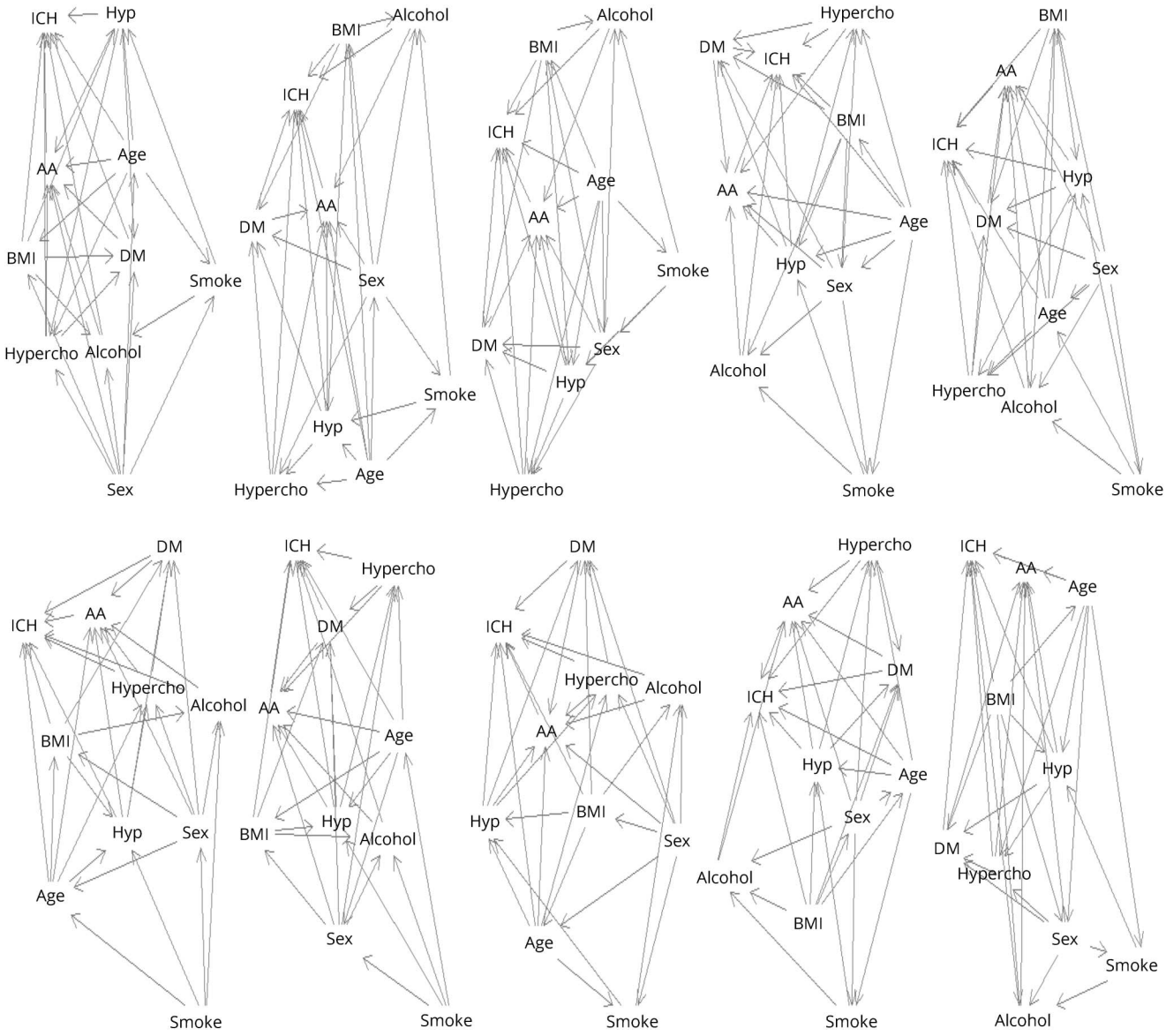
After adjusting for the variables in the first selected MSA set (age, BMI, hypertension, sex), heavy alcohol intake turned out to be associated with the subgroup of patients with deep ICH (OR, 1.68; 95% CI, 1.36–2.09) as well as with the whole group of cases (OR, 1.38; 95% CI, 1.17–1.63), while we did not detect any relation with the subgroup of patients with lobar ICH (OR, 1.01; 95% CI, 0.77–1.32; table 4). Adjustment for the variables in the second selected MSA set (BMI, sex, smoking) gave similar results (not shown).

To verify the robustness of our results, we performed a further logistic regression after excluding subjects with cerebellar hematoma (n = 72) and corresponding controls from the case-control analysis of patients with lobar ICH, as a sensitivity analysis. Findings were similar to those of the main analysis; heavy alcohol intake was unrelated to the risk of bleeding isolated to the cerebral cortex and subcortical white matter (OR, 1.07; 95% CI, 0.82–1.40).

Discussion

The main finding of the present analysis is that excessive alcohol consumption might exert a causal effect on the occurrence of ICH in older individuals. The effect of alcohol appears, in particular, to be more prominent on the arteriolosclerotic process involving deeply located cerebral small vessels than on cerebral amyloid angiopathy–related disease. This supports the prevailing hypothesis of a differential response to alcohol according to the underlying vessel pathology. In this regard, our findings are in line with those observed in the setting of case-only studies conducted on cohorts of European[14] and Asian[15] patients, which pointed toward an active role of alcohol in the biology of cerebral small vessel disease. More recently, results of the multiethnic Ethnic/Racial Variations of Intracerebral

Figure 2 Graphical representation of the set of statistically equivalent directed acyclic graphs



AA = antiplatelet agents; BMI = body mass index; DM = diabetes mellitus; Hyp = hypertension; Hypercho = hypercholesterolemia; ICH = intracerebral hemorrhage.

Hemorrhage (ERICH) case-control study[16] demonstrated an association between heavy alcohol intake and deep ICH in subgroups of black and Hispanic patients. These studies thus reinforce the idea that excessive alcohol consumption is likely a risk factor for this subtype of cerebral bleeding, especially in some ethnic groups. Our analysis confirmed the observations in the latter study, but also extended its results, as we detected a likely causal relation between a high amount of alcohol intake and deep ICH in white Caucasian patients. Furthermore, because our study focused on a subgroup of elderly patients, unlike the analysis conducted on the ERICH database, it seems reasonable that these effects also occur beyond younger age.[14,16]

What further distinguishes our study from others, and should be regarded as a strength of the present analysis, is the application of DAGs, a useful tool in social and epidemiologic research for making causal inferences from observational data when investigating the relationship between exposure and outcome.[7,8] This allowed us to overcome a methodologic limitation of the previous studies on this topic, that is, the application of the traditional confounding adjustment for the analysis of data. Inference on any causal relation between alcohol consumption and ICH is, actually, dealt with by adjusting for differing characteristics between exposed and nonexposed in multivariable regression models. Such approaches, in which every variable associated with outcome and exposure is entered into the analysis as a confounder separately, however, do not allow adequate evaluation of confounding. Determining which variables need to be adjusted for in order to remove confounding is challenging and can sometimes influence the results

Table 3 Baseline and clinical characteristics of the study group

	All ICH			Lobar ICH			Deep ICH		
	Cases (n = 3,173)	Controls (n = 3,155)	*p* Value	Cases (n = 1,471)	Controls (n = 1,464)	*p* Value	Cases (n = 1,702)	Controls (n = 1,691)	*p* Value
Age, y	75.79 ± 9.65	73.18 ± 7.28	≤0.001	76.45 ± 9.49	73.67 ± 7.21	≤0.001	75.22 ± 9.76	72.75 ± 7.32	≤0.001
Sex, males	1,760 (55.5)	1,747 (55.4)	0.939	781 (53.1)	775 (52.9)	0.933	979 (57.5)	972 (57.5)	0.981
Body mass index, ≥30 kg/m^2	1,061 (36.9)	1,109 (35.2)	0.124	501 (36.3)	498 (34.0)	0.207	560 (37.4)	611 (36.1)	0.447
Coronary artery disease	557 (17.6)	270 (8.6)	≤0.001	283 (19.3)	125 (8.7)	≤0.001	275 (16.2)	145 (8.7)	≤0.001
Previous atrial fibrillation	479 (15.1)	74 (2.3)	≤0.001	246 (16.8)	34 (2.3)	≤0.001	232 (13.6)	40 (2.4)	≤0.001
Hypertension			≤0.001			≤0.001			≤0.001
Nonhypertensive	742 (23.4)	1,287 (40.8)		371 (25.2)	595 (40.6)		371 (21.8)	692 (40.9)	
Hypertensive under treatment	2,049 (64.7)	1,778 (56.4)		953 (64.8)	828 (56.6)		1,096 (64.5)	950 (56.2)	
Hypertensive not under treatment	378 (11.9)	90 (2.9)		146 (9.9)	41 (2.8)		232 (13.7)	49 (2.9)	
Diabetes			≤0.001			≤0.001			≤0.001
Nondiabetic	2,559 (80.8)	2,740 (86.8)		1,202 (81.8)	1,279 (87.4)		1,357 (79.9)	1,461 (86.4)	
Diabetic under treatment	513 (16.2)	379 (12.0)		231 (15.7)	167 (11.4)		282 (16.6)	212 (12.5)	
Diabetic not under treatment	97 (3.1)	36 (1.1)		37 (2.5)	18 (1.2)		60 (3.5)	18 (1.1)	
Hypercholesterolemia			≤0.001			≤0.001			≤0.001
Nonhypercholesterolemic	2,357 (74.4)	2,226 (70.6)		1,100 (74.9)	1,028 (78.2)		1,256 (73.9)	1,198 (70.8)	
Hypercholesterolemic under treatment with statins	564 (17.8)	426 (13.5)		269 (18.3)	200 (13.7)		295 (17.4)	226 (13.4)	
Hypercholesterolemic not under treatment with statins	247 (7.8)	503 (15.9)		99 (6.7)	236 (16.1)		148 (8.7)	267 (15.8)	
Current smoking	345 (10.9)	342 (10.8)	0.89	139 (9.5)	144 (9.8)	0.778	206 (12.2)	198 (11.7)	0.676
Antiplatelet agents	1,099 (34.6)	505 (16)	≤0.001	537 (36.6)	233 (15.9)	≤0.001	562 (33.1)	272 (16.1)	≤0.001
Oral anticoagulants	420 (13.2)	30 (1)	≤0.001	232 (15.8)	14 (1)	≤0.001	188 (11.1)	16 (0.9)	≤0.001
Alcohol, heavy intake	427 (14.2)	415 (13.2)	0.232	156 (11.3)	185 (12.6)	0.287	270 (16.6)	230 (13.6)	0.016

Abbreviation: ICH = intracerebral hemorrhage.
Data represent mean ± SD or n (%).

Table 4 Multivariable odds ratios for ICH by location

	All ICH	Lobar ICH	Deep ICH
Age, y	1.35 (1.26–1.45)	1.40 (1.26–1.56)	1.32 (1.20–1.45)
Sex, males	1.02 (0.91–1.15)	1.01 (0.85–1.21)	1.03 (0.87–1.20)
Hypertension	2.21 (1.87–2.40)	1.76 (1.46–2.11)	2.50 (2.10–2.57)
Body mass index, ≥30 kg/m^2	2.08 (1.81–2.38)	2.56 (2.08–3.12)	1.81 (1.53–2.17)
Alcohol, heavy intake	1.38 (1.17–1.63)	1.01 (0.77–1.32)	1.68 (1.36–2.09)

Abbreviation: ICH = intracerebral hemorrhage.
Data represent odds ratio (95% confidence interval).

of the analysis.[17] Another advantage of using the DAG approach is that the model requires only a subset of covariates, among those associated with exposure and outcome, to obtain an unbiased estimate of effect. This implicates more degrees of freedom and, therefore, increased statistical efficiency of the analysis.[18] These aspects should be kept in mind when considering that there are obvious ethical concerns in conducting a randomized controlled trial on the relation between alcohol consumption and the risk of stroke, and any recommendations in this regard depend, therefore, on the quality of data from observational studies.

There are also some notable limitations to our study. First, alcohol consumption was measured by self-reported alcohol drinking habit, which is subject to recall bias. Also, because we dichotomized subjects into heavy drinkers and light to moderate drinkers or nondrinkers, we lack information about the relationship between alcohol intake and ICH rate in other categories of alcohol consumption. Second, the hospital-based setting of our study prevents the possibility of knowing the exact blood pressure values, as well as serum cholesterol and glucose levels, just before ICH occurrence. Despite these potential drawbacks, based on our findings and, indirectly, on those from previous studies, it is reasonable to conclude that high alcohol intake might exert a causal effect on ICH. This is mainly due to its effect on deeply located cerebral small arteries and extends beyond younger age.

Author contributions

Dr. Alessandro Pezzini had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Paolo Costa, Mario Grassi, Alessandro Pezzini. Acquisition of data: all authors. Interpretation of data: Paolo Costa, Mario Grassi, Alessandro Pezzini. Drafting of the manuscript: Paolo Costa, Alessandro Pezzini. Critical revision of the manuscript for important intellectual content: all authors. Data analysis: Paolo Costa, Alessandro Pezzini. Statistical analysis: Mario Grassi. Administrative, technical, or material support: Alessandro Pezzini. Study supervision: Alessandro Padovani, Alessandro Pezzini.

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