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Association between heavy alcohol consumption and cryptogenic ischaemic stroke in young adults: a case–control study

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ABSTRACT

Background The underlying risk factors for young-onset cryptogenic ischaemic stroke (CIS) remain unclear. This multicentre study aimed to explore the association between heavy alcohol consumption and CIS with subgroup analyses stratified by sex and age.

Methods Altogether, 540 patients aged 18–49 years (median age 41; 47.2% women) with a recent CIS and 540 sex-matched and age-matched stroke-free controls were included. Heavy alcohol consumption was defined as >7 (women) and >14 (men) units per week or at least an average of two times per month ≥5 (women) and ≥7 (men) units per instance (binge drinking). A conditional logistic regression adjusting for age, sex, education, hypertension, cardiovascular diseases, diabetes, hypercholesterolaemia, current smoking, obesity, diet and physical inactivity was used to assess the independent association between alcohol consumption and CIS.

Results Patients were twice as more often heavy alcohol users compared with controls (13.7% vs 6.7%, p<0.001), were more likely to have hypertension and they were more often current smokers, overweight and physically inactive. In the entire study population, heavy alcohol consumption was independently associated with CIS (adjusted OR 2.11; 95% CI 1.22 to 3.63). In sex-specific analysis, heavy alcohol consumption was associated with CIS in men (2.72; 95% CI 1.25 to 5.92), but not in women (1.56; 95% CI 0.71 to 3.41). When exploring the association with binge drinking alone, a significant association was shown in the entire cohort (2.43; 95% CI 1.31 to 4.53) and in men (3.36; 95% CI 1.44 to 7.84), but not in women.

Conclusions Heavy alcohol consumption, particularly binge drinking, appears to be an independent risk factor in young men with CIS.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The incidence of young-onset ischaemic stroke (IS) is increasing, and this increase seems to be driven by the proportion of cryptogenic IS (CIS). Habitual risk factors, such as heavy alcohol consumption and binge drinking, seem more important in younger vs older individuals, but their association with young-onset CIS still remains understudied.

WHAT THIS STUDY ADDS

⇒ Our multicentre case–control Searching for Explanations for Cryptogenic Stroke in the Young: Revealing the Etiology, Triggers and Outcome study demonstrated a strong association between heavy alcohol consumption and binge drinking and young-onset CIS, particularly in men, independent from coexisting stroke risk factors.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Future studies should more extensively explore the mechanisms and associated features increasing the risk of young-onset CIS in individuals with heavy drinking. Reducing heavy alcohol consumption remains one of the main targets of lifestyle interventions in young individuals to mitigate their risk of IS, including CIS.

INTRODUCTION

Large studies from the last decade have demonstrated a high prevalence of traditional risk factors in young patients with ischaemic stroke (IS).[1–3] There is evidence to suggest that also habitual risk factors may have a stronger role in the development of stroke in younger compared with older individuals. A German nationwide case–control study indicated that low physical activity and hypertension had the strongest association for young-onset IS, followed by smoking and heavy episodic alcohol consumption.[4] Interestingly also, a more recent prospective population-based incidence study

suggested that the increase in the incidence of young-onset IS over the last decades was mainly driven by strokes in individuals without traditional risk factors and with undetermined causes.[5]

Alcohol intoxication has long been known to be associated with young-onset IS.[6] Both recent and long-term heavy alcohol consumption, as well as binge drinking, can act as a chronic risk factor[7 8] and as a transient trigger[9] for young-onset IS. With long-term heavy drinking, up to 8–15 fold increases in the stroke risk in young patients have been shown.[7 8] In the Risk Factors for Ischemic and Intracerebral Hemorrhagic Stroke in 22 Countries (INTERSTROKE) study, a subgroup analysis of non-selected young patients with IS reported a 5-fold increased risk associated with binge drinking.[10]

There is a special interest in studying risk factors for cryptogenic IS (CIS) as (1) they seem to drive the increasing incidence, (2) habitual risk factors seem more important in younger vs older individuals, (3) many other young-specific risk factors and lifestyle habits may have synergy with heavy alcohol consumption and binge drinking and (4) different patterns of alcohol consumption have not been assessed in a larger sample of young patients with CIS. In this study, we aimed to explore the association between heavy alcohol consumption and young-onset CIS in an international multicentre case–control study.

METHODS

Study population

Between November 2013 and November 2022, 546 young patients with CIS and 546 sex-matched and age-matched stroke-free control subjects were enrolled in 19 European centres in the prospective multicentre SECRETO study (Searching for Explanations for Cryptogenic Stroke in the Young: Revealing the Etiology, Triggers and Outcome, NCT01934725). Patients aged 18–49 years and hospitalised due to first-ever imaging-positive IS of undetermined aetiology were included and examined according to a standardised protocol, as previously described.[11 12]

All included patients underwent standardised and timely diagnostic workup to exclude definite causes of stroke. Investigations included brain MRI, imaging of intracranial and extracranial vessels with either CT angiography or MR angiography, laboratory testing per protocol, 12-lead ECG, continuous ECG for at least 24 hours, as well as both transthoracic echocardiogram and transoesophageal echocardiogram (TEE). Echocardiography studies were performed according to a standardised protocol.[13] Ancillary testing was carried out on the discretion of physician in charge. Stroke severity was reported with the National Institutes of Health Stroke Scale (NIHSS) score.

CIS was defined according to A-S-C-O classification as the absence of disease (grade 0), or any of grade II (causality uncertain) or grade III (unlikely a direct cause) pathology using diagnostic testing of highest grade of evidence.[14]

One sex-matched and age-matched (±5 years) stroke-free control for each patient from the same region was searched locally at each study centre. Sources to identify control subjects included a random search through population registers where feasible, patients' non-related proxies and hospital staff unrelated to the study.

Cardiovascular risk factors and comorbidities

Detailed clinical history was obtained from all participants using medical records and a structured interview during a study visit. Low level of education was classified as either primary or lower secondary education, or upper secondary education. Registered cardiovascular risk factors included hypertension (prior diagnosis of hypertension, prior antihypertensive medication or a mean of two office blood pressure measures 140/90 or over at study visit), diabetes mellitus (prior diagnosis of any diabetes and/or prior antidiabetic medication), hypercholesterolaemia (prior diagnosis of hypercholesterolaemia or antilipemic medication), cardiovascular disease (history of coronary heart disease, congestive heart failure, peripheral arterial disease or atrial fibrillation (AF)), current tobacco smoking (smoking at least one cigarette per day on average), waist-to-hip ratio (obesity defined as >0.85 in women and >0.90 in men), unhealthy diet, physical inactivity and heavy alcohol consumption. Physical inactivity was assessed using the short version of the International Physical Activity Questionnaire,[15] defined as not meeting any of the criteria for either moderate or high levels of physical activity. A modified version of the Mediterranean Diet Score was used to report participants' diets, with a higher score indicating a healthier diet and a median of 24 points used as the cut-off for the dichotomous variable.[16]

Adaptation of the WHO Alcohol, Smoking and Substance Involvement Screening Test was used to assess alcohol consumption with a structured interview both in patients and controls.[17] Heavy alcohol consumption was defined as >7 (women) and >14 (men) units per week or at least an average of two times per month ≥5 (women) and ≥7 (men) units per instance (binge drinking), according to Substance Abuse and Mental Health Services Administration (SAMHSA), US Department of Health and Human Services.[18]

For this study, high-risk right-to-left shunt (RLS) was defined as PFO combined with atrial septal aneurysm in TEE, or a large shunt either in TEE or in transcranial Doppler with bubble study (TCD-BS).[13 19] A subcohort of stroke-free controls at selected study sites also underwent evaluation for RLS.

Statistical analysis

Univariate comparisons of baseline characteristics between patients and controls were assessed using statistical testing appropriate for matched case–control studies, for example, McNemar's test for dichotomised variables, Paired t-test to compare normally distributed continuous variables, and Wilcoxon signed rank test for non-normally distributed continuous variables. Results are presented as absolute numbers (percentage), mean (SD or median (IQR). A $p<0.05$ was considered significant.

Data imputation was performed for variables with >10 missing values, namely waist circumference (percentage missing, 8.4%), hip circumference (8.7%) and diet score (14.9%). Multivariate imputation was performed with a Chained Equations R package. In the controls' variables, there were no variables with >10 missing values and thus, no imputation was performed.

Any potential imbalances between patients and controls were addressed using conditional logistic regression analysis suitable for a matched case–control study, and adjusted OR and 95% CI were reported. Three models are presented: (1) unadjusted conditional logistic regression analysis, (2) adjusted for age, sex and level of education and (3) fully adjusted for age, sex, level of education and predefined vascular risk factors. Based on previous literature, potential confounding vascular risk factors included hypertension, hypercholesterolaemia any type of diabetes mellitus, current smoking, obesity, physical inactivity, unhealthy diet and any other cardiovascular disease. To explore any potential dose–response relationship between alcohol consumption and CIS, we performed additional exploratory conditional logistic regression analysis with quartiles of alcohol consumption, lowest quartile used as the reference group.

We studied potential interactions between heavy alcohol consumption, sex, age and the presence or absence of selected comorbidities, including current smoking, obesity, physical inactivity and high-risk RLS in a logistic regression model adjusted for age, sex, level of education and vascular risk factors by including the presence of the comorbidity as a covariate and further including an interaction term in the model.

Additional conditional logistic regression analyses with similar models were performed to explore the association stratified by sex for binge drinking alone with young-onset CIS. As an exploratory analysis, these were also performed for three predetermined age groups as well (18–34, 35–44 and 45–49 years).

Furthermore, to explore the robustness of the results, we assessed the association by comparing patients to controls who were identified strictly from population-based sources, that is, excluding those selected from for example, hospital staff and patients' nonrelated proxies. This sensitivity analysis is also reported stratified by sex.

Statistical analyses were performed with IBM SPSS Statistics for Windows, V.29.0 (IBM).

RESULTS

To study associations, we included 540 patients with CIS (median age 41 years, IQR 34–46; 47.2% women) and 540 age-matched and sex-matched controls with detailed data on alcohol consumption available. In patients, the median delay from symptom onset to hospital admission was 0 (IQR 0–1) days and from admission to study inclusion/interview 6 (IQR 4–9) days. Median NIHSS score on admission was 2 (IQR 0–4, range 0–17). Of all patients, 25.7% had NIHSS score of 0, 50.6% had mild strokes (NIHSS 1–4), 14.0% had moderate strokes (NIHSS 5–9) and 9.9% had severe strokes (NIHSS≥10). Patients with heavy alcohol consumption had more severe strokes compared with patients without heavy alcohol consumption (mild strokes 44.6% vs 51.4%, moderate strokes 24.3% vs 12.3% and severe strokes 12.2% vs 9.5%, p=0.027).

Univariate comparison between patients and matched controls

In the entire study population, patients were more likely to be heavy alcohol users compared with controls (13.7% vs 6.7%, p<0.001) (table 1 and figure 1). Case–control analyses stratified by age groups showed that this difference was significant in men aged 18–34 years (32.3% vs 11.3%, p=0.004) but not in other age groups (online supplemental figure s1). Regarding other risk factors, patients were more likely to have a history of hypertension, and they were more often current smokers, overweight, less educated, physically inactive and had more unhealthy diet (table 1). Overall, there were very few participants with pre-existing cardiovascular disease.

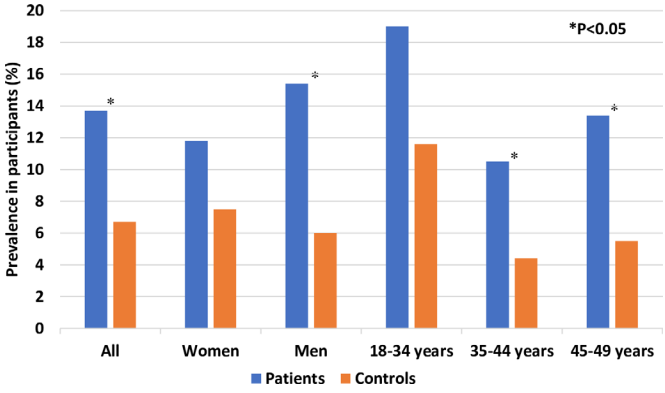

Figure 1 Comparison of heavy alcohol consumption for all study participants and stratified by sex and age group.

Female patients had a lower level of education and more unhealthy diet compared with female controls. They were also more likely to be current smokers, obese and hypertensive. There was no difference in heavy alcohol consumption (11.8% vs 7.5%, p=0.099). Male patients were more frequently heavy alcohol users compared with male controls (15.4% vs 6.0%, p<0.001). Male patients also had a lower level of education, more unhealthy diet, they were more often obese, and current smokers (table 1). In patients, the youngest males were more likely to be heavy alcohol users compared with other age groups (p<0.001) (online supplemental figure s1). In female patients, there were no significant differences between age groups.

Table 1 Comparison of baseline characteristics of cardiovascular risk factors of young cryptogenic ischaemic stroke patients and stroke-free control subjects included in the study

	All		Women		Men	
Characteristic (No. of patients/controls with missing data if applicable)	Patients (n=540)	Controls (n=540)	Patients (n=255)	Controls (n=255)	Patients (n=285)	Controls (n=285)
Age	41 (34–46)	41 (34–46)	40 (31–45)	41 (31–45)	42 (36–46)	42 (35–47)
Low level of education (2/4)	297 (55.2)	189 (35.3)*	133 (52.4)	88 (34.6)*	164 (57.7)	101 (35.8)*
Heavy alcohol consumption	74 (13.7)	36 (6.7)*	30 (11.8)	19 (7.5)	44 (15.4)	17 (6.0)*
Binge drinking	63 (11.7)	26 (4.8)*	20 (7.8)	12 (4.7)	43 (15.1)	14 (4.9)*
Hypertension (0/4)	187 (34.6)	144 (26.9)*	81 (31.8)	53 (21.0)*	106 (37.2)	91 (32.0)
Diabetes mellitus (0/1)	16 (3.0)	10 (1.9)	6 (2.4)	0(0)	10 (3.5)	10 (3.5)
Hypercholesterolaemia (0/2)	12 (2.2)	25 (4.6)*	2 (0.8)	4 (1.6)	10 (3.5)	21 (7.4)*
Cardiovascular disease†	5 (0.9)	3 (0.6)	2 (0.8)	0(0)	3 (1.1)	3 (1.1)
Unhealthy diet (0/5)	276 (51.4)	196 (36.6)*	119 (47.0)	74 (29.2)*	157 (55.3)	122 (43.3)*
Current tobacco smoking (3/3)	176 (32.8)	81 (15.1)*	70 (27.7)	38 (14.9)*	106 (37.3)	43 (15.2)*
Physical inactivity (6/7)	159 (29.8)	123 (23.1)*	83 (32.8)	64 (25.4)	76 (27.0)	59 (21.0)
Abdominal obesity (0/6)	321 (59.4)	237 (44.4)*	110 (43.1)	63 (25.0)*	211 (74.0)	174 (61.7)*

Data are n (%) or median (IQR).
McNemar's test was applied for comparison for categorical variables and Wilcoxon signed-rank test for continuous non-parametric variables.
*p<0.05
†Cardiovascular disease includes any of coronary heart disease, chronic heart failure, peripheral arterial disease or history of myocardial infarction.

Table 2 ORs and 95% CI from conditional logistic regression on the association between heavy alcohol consumption, binge drinking and cryptogenic ischaemic stroke, also stratified by sex

	Model 1: unadjusted		Model 2: adjusted for age, sex and level of education.		Model 3: adjusted for age, sex, level of education and all vascular risk factors*	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
All (540 pairs)						
Heavy alcohol consumption	2.56 (1.61 to 4.06)	<0.001	2.27 (1.38 to 3.74)	0.001	2.11 (1.22 to 3.63)	0.007
Binge drinking	3.06 (1.80 to 5.20)	<0.001	2.73 (1.53 to 4.85)	<0.001	2.43 (1.31 to 4.53)	0.005
Men (285 pairs)						
Heavy alcohol consumption	3.25 (1.70 to 6.21)	<0.001	3.11 (1.53 to 6.30)	0.002	2.72 (1.25 to 5.92)	0.012
Binge drinking	4.22 (2.04 to 8.73)	<0.001	4.17 (1.87 to 9.28)	<0.001	3.36 (1.44 to 7.84)	0.005
Women (255 pairs)						
Heavy alcohol consumption	1.85 (0.94 to 3.63)	0.075	1.58 (0.77 to 3.25)	0.215	1.56 (0.71 to 3.41)	0.267
Binge drinking	1.89 (0.84 to 4.24)	0.123	1.49 (0.62 to 3.54)	0.371	1.50 (0.58 to 3.92)	0.404

Binge drinking is defined as an average of two times per month ≥5 (women) and ≥7 (men) units of alcohol per time.
*P for interaction between heavy alcohol consumption and sex 0.038.

Association between heavy alcohol consumption and CIS

In the unadjusted model, a significant association between heavy alcohol consumption and young-onset CIS in the entire study population emerged (OR 2.56; 95% CI 1.61 to 4.06, p<0.001). This association remained significant after adjustment for demographics (OR 2.27; 95% CI 1.38 to 3.74, p=0.001) and for further vascular risk factors (OR 2.11; 95% CI 1.22 to 3.63, p=0.007) (table 2, figure 2). ORs and 95% CIs for each covariate appear in online supplemental table s1.

Association between heavy alcohol consumption and CIS according to sex

In sex-specific analysis, the association between heavy alcohol consumption and CIS was significant in men, both in unadjusted analysis (OR 3.25; 95% CI 1.70 to 6.21, p<0.001) and when analysed further adjusting for demographics (OR 3.11; 95% CI 1.53 to 6.30, p=0.002) and for demographics and vascular risk factors (OR 2.72; 95% CI 1.25 to 5.92, p=0.012) (table 2, figure 2, p for interaction 0.038). No association was found in women alone when adjusting for demographics (OR 1.58; 95% CI 0.77 to 3.25, p=0.215), nor in a fully adjusted model including demographics and vascular risk factors (OR 1.56; 95% CI 0.71 to 3.41, p=0.267) (table 2, figure 2). ORs and 95% CIs for each covariate are shown in online supplemental table s2. In an exploratory analysis of men by age groups, in the youngest men, a significant association was shown between heavy alcohol consumption and CIS (OR 12.11; 95% CI 1.54 to 95.47, p=0.018) (online supplemental table s3). However, there was no formal interaction between heavy alcohol consumption and age group in men (p for interaction 0.665). No association was seen in other age groups in men or any age group in women.

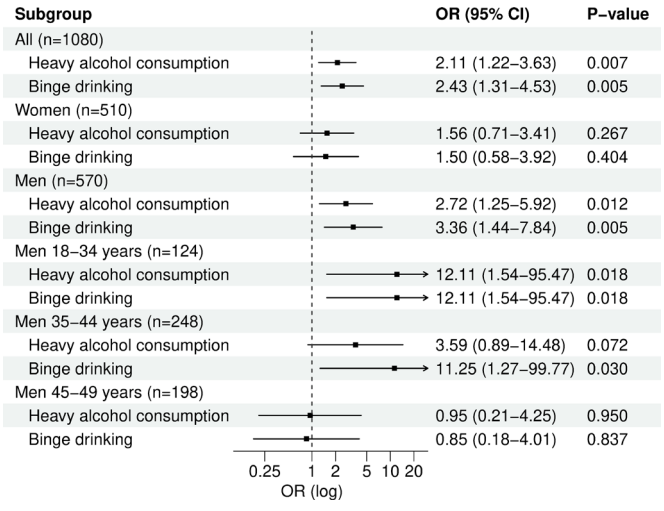

Figure 2 Association between heavy alcohol consumption and cryptogenic ischaemic stroke, stratified by sex and age (for men only). Diabetes and cardiovascular disease included in the model only in older men (45–49 years) due to low prevalence of these risk factors in other groups.

Association between binge drinking and CIS

Analysis of binge drinkers alone showed similar differences in univariate comparison in the entire study population (11.7% vs 4.8%, p<0.001) and in men (15.1% vs 4.9%, p<0.001) but not in women (figure 3). Association with young-onset CIS was also significant in the entire population (fully adjusted OR 2.43; 95% CI 1.31 to 4.53, p=0.005) and in men (fully adjusted OR 3.36; 95% CI 1.44 to 7.84, p=0.005), but again, not in women (fully adjusted OR 1.50; 95% CI 0.58 to 3.92, p=0.404) (table 2, figure 2). Unadjusted and less-adjusted models and ORs for each covariate are shown in online supplemental tables s4 and s5.

Interaction assessment with other risk factors

In the entire cohort, there was no interaction between heavy alcohol consumption and current smoking (p=0.667), obesity (p=0.732) or physical inactivity (p=0.295) (table 3). In men,

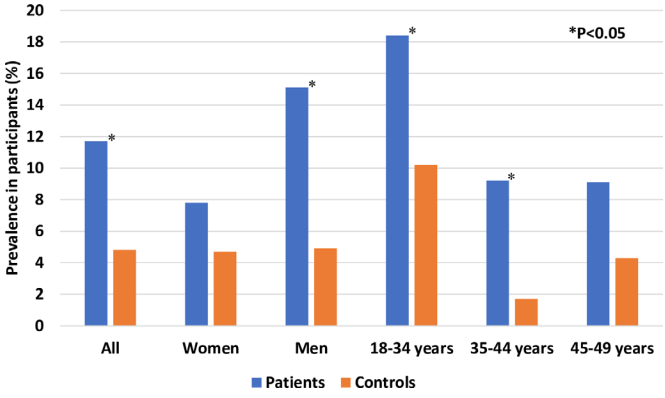

Figure 3 Comparison of binge drinking for all study participants and stratified by sex and age group.

Table 3 Exploratory subgroup analyses on the association between heavy alcohol consumption and cryptogenic ischaemic stroke

	Participants with heavy consumption No. patients/no. controls	Participants without heavy consumption No. patients/no. controls	Unadjusted OR (95% CI)	P for interaction*
All participants				
Current smoking				0.667
No	30/19	331/437	2.10 (1.16 to 3.80)	
Yes	43/15	133/66	1.42 (0.74 to 2.75)	
Obesity				0.732
No	30/18	189/279	2.49 (1.35 to 4.59)	
Yes	44/18	277/219	1.94 (1.09 to 3.46)	
Physical inactivity				0.295
No	50/29	325/381	2.03 (1.26 to 3.28)	
Yes	22/5	137/118	3.85 (1.42 to 10.49)	
Men				
Current smoking				0.968
No	15/9	163/230	2.36 (1.01 to 5.52)	
Yes	29/6	77/37	2.32 (0.89 to 6.08)	
Obesity				0.056
No	16/5	58/103	5.68 (1.98 to 16.31)	
Yes	28/12	183/162	2.08 (1.02 to 4.22)	
Physical inactivity				0.852
No	32/12	173/210	3.22 (1.61 to 6.44)	
Yes	11/3	65/56	3.27 (0.87 to 12.31)	
Women				
Current smoking				0.509
No	15/10	168/207	1.88 (0.82 to 4.28)	
Yes	14/9	56/29	0.81 (0.31 to 2.08)	
Obesity				0.372
No	14/13	131/176	1.47 (0.67 to 3.24)	
Yes	16/6	94/57	1.62 (0.60 to 4.37)	
Physical inactivity				0.100
No	18/17	152/171	1.21 (0.60 to 2.44)	
Yes	11/2	72/62	4.74 (1.01 to 22.19)	

*P value from adjusted logistic regression with an interaction term. Covariates included age, hypercholesterolaemia, hypertension, current tobacco smoking, physical inactivity, heavy alcohol consumption, obesity, diabetes mellitus and cardiovascular disease. For women, diabetes and cardiovascular disease were left out due to very low prevalence.

we found no interaction between heavy alcohol consumption and current smoking (p=0.968), obesity (p=0.056) or physical inactivity (p=0.852). In women, no interaction between heavy alcohol consumption and current smoking (p=0.509), obesity (p=0.372) or physical inactivity (p=0.100) was found (table 3). High-risk RLS was detected in 194 (37.9%) patients and 34 (8.8%) controls (p<0.001) of the investigated individuals. No difference in the prevalence of high-risk RLS among patients was observed between sexes (women 39.3% vs men 35.9%, p=0.419) or in controls (women 7.9% vs men 10.1%, p=0.466). Exploratory analysis showed no interaction between heavy alcohol consumption and high-risk RLS (p=0.108) (online supplemental table s6).

Sensitivity analyses

When selecting case–control pairs with strictly population-based controls (n=316), patients with heavy alcohol consumption had a higher risk of CIS (unadjusted OR 2.25; 95% CI 1.50 to 4.05, p=0.007). The association remained significant when adjusted for demographics (OR 2.22; 95% CI 1.15 to 4.27, p=0.017), but not in the fully adjusted model (OR 1.97; 95% CI 0.94 to 4.10, p=0.071). In male patients with population-based male controls only, the association remained significant when adjusted for demographics (OR 3.13; 95% CI 1.29 to 7.58, p=0.012), but not in the fully adjusted model (OR 2.39; 95% CI 0.87 to 6.54, p=0.091). In women, no association was observed in any of the models. Unadjusted and less-adjusted models and ORs for each covariate are shown in online supplemental tables s7 and s8. Again, in univariate analyses, particularly younger male patients were more likely to be binge drinkers than young male controls (online supplemental table s3 and online supplemental figure s2). No dose-response was observed in further exploratory analysis in the entire study population nor in men alone (online supplemental table s9).

DISCUSSION

In this multicentre case–control study, we detected a robust independent association between heavy alcohol consumption and binge drinking with young-onset CIS. This connection held true in young men, even after accounting for various well-known confounding factors, such as hypertension, physical inactivity, obesity and current smoking. Interestingly, this association was not observed in young women.

The present analysis adds to previous knowledge from meta-analysis of the associations between alcohol consumption and stroke by demonstrating that high alcohol consumption as well as binge drinking is an independent risk factor for IS, particularly in young men.[20–22] In smaller and older studies, both recent and long-term heavy alcohol consumption, as well as binge drinking,

have been shown to act as a chronic risk factor[7 8] and as a transient trigger[9] for young-onset IS of any aetiology. With long-term heavy drinking, increases of up to 8–15 times in the stroke risk in young patients have been reported.[7 8 22] However, most of these studies included young IS patients with any type of aetiology, in contrast to a specific subgroup of CIS patients in our study.

In accordance with our findings, patients who were current drinkers in prior studies were more likely to be younger men, but also current smokers. This reflects reality, as for instance according to Centers for Disease Control and Prevention, heavy alcohol consumption and binge drinking are most common among younger adults aged 18–34 and among men. Furthermore, the INTERSTROKE study reported risk factors for a subgroup of young patients (<45 years) alone, such as a 5.4-fold risk for binge drinking stroke (71% were IS).[10] However, the INTERSTROKE study included IS of all aetiologies, in contrast to subgroups of CIS patients in our study. Also, the Stroke in Young Fabry Patients study reported that among patients with transient ischaemic attack or IS of any aetiology, heavy alcohol consumption was more common in men than in women, highlighted in individuals aged 18–24 years compared with other age groups.[2] The independent relation with heavy alcohol consumption only in men in our study might be explained by the higher prevalence of heavy alcohol consumption and binge drinking compared with female patients. Particularly binge drinking might further be associated with other less well-documented risk factors in men, such as illicit drug use and unhealthy diet. In our study, female patients also had other more frequent risk factors compared with female controls, namely hypertension and abdominal obesity. Other well-known risk factors in women include pregnancy, puerperium and the use of combined oral contraceptives. These sex-specific and gender-specific risk factors might diminish the effect of alcohol consumption alone compared with young men.

Several differing criteria for heavy alcohol consumption and binge drinking exist. Applying different criteria in different studies may evidently affect the comparison between studies. For instance, in the INTERSTROKE study, the limits for a high intake of alcohol were considerably higher than in the SECRETO study, >14 drinks for women and >21 drinks for men.[23] Binge drinking was defined as >5 drinks in 1 day at least once a month over the previous 12 months for both sexes. Their study referred to an older prospective population-based study and criteria from 1997,[24] compared with SAMHSA criteria used in SECRETO which were updated in 2015. This difference shows that the criteria have become considerably stricter over the years.

Mechanisms associated with heavy alcohol consumption and CIS include, for instance, adverse effects on hemostasis, fibrinolytics, blood clotting and subclinical cardiac arrhythmias, excluding documented AF.[25] Heavy drinkers may also be more likely to suffer from head and neck trauma predisposing cervical or intracranial artery dissection and subsequent IS, although such mechanisms are not likely in CIS. Moreover, excessive alcohol consumption can predispose other risk factors including hypertension and visceral obesity, but also more acute conditions such as cerebral vasospasm.[26 27] In our study, patients with heavy alcohol consumption also had more severe strokes based on unknown mechanisms. This might be caused by a potential covert embolism from heart or other unknown source or perhaps thrombus developing locally in larger arteries. Recent analyses of first SECRETO including 150 patients and controls also demonstrated that left atrial myopathy more than doubled the risk of young-onset CIS, but LA myopathy was not associated with heavy alcohol consumption itself.[28] Heavy drinkers may also harbour several other risk factors making them as potentially important target group for both primary and secondary preventive measures.

The most notable strengths of the SECRETO study include the robustness of the prespecified and published study protocol and an extensive and timely diagnostic workup for each participant. As described above, only patients with imaging verified IS were included to ensure the homogeneity of the study population and to exclude any stroke mimics. Furthermore, all participants were examined in a standardised manner and validated, structured questionnaires were used for data collection with high granularity. There were only a few missing data points, as patients and controls were personally interviewed. Sensitivity analyses were performed to demonstrate the robustness of the results, such as including only population-based controls. It was also possible to adjust for multiple relevant confounders in the multivariable analyses. As this study enrolled patients and controls in 19 centres across Europe, our results are considered generalisable to populations of European origin.

However, some limitations must be acknowledged. Although the aim was to enrol all consecutive patients, some selection bias might have occurred. For instance, as enrolled patients had relatively mild strokes on admission, it is possible that some patients with more debilitating symptoms may have been left out and thus, the results of this study are generalisable to minor to moderate strokes. However, prior studies have demonstrated that young IS patients tend to have overall lower NIHSS on admission than older patients.[29] Some selection bias might also be present when enrolling controls. For instance, controls with more frequent alcohol consumption might have been less willing to participate in this kind of study, possibly leading to overestimation of effect size. Our sensitivity analysis showed, however, that when restricting to population-based controls only, the effect size of heavy alcohol consumption remained similar and nearly significant even with a smaller sample size. As informed consent also from controls was required before collecting more data on baseline characteristics and risk factors, we were not able to describe in detail those stroke-free individuals who did not accept our study invitation. However, the prevalence of heavy alcohol consumption reported by SAMHSA was comparable with the prevalence in stroke-free controls in our study (7.1% in young adults aged 18 to 25 and 6.3% in adults aged 26 or older),[17] further supporting that there is no considerable selection bias with our control subjects. As the data for this study were collected mainly during hospitalisation or shortly after discharge, we were not able to report the frequency of, for instance, newly-onset AF later diagnosed with an implantable loop recorder (ILR) or home telemetry. However, the use of ILRs and external ECG recorders have become more prevalent only in recent years and were seldom used during our study's recruitment. In addition, there are no strong recommendations to use of ILRs for screening AF in young stroke patients given their low expected yield.

CONCLUSIONS

Our multicentre case–control study demonstrated a strong association between heavy alcohol consumption and binge drinking and young-onset CIS, independent from coexisting stroke risk factors. Subgroup analyses confirmed these associations in men but not in women. Future studies should more extensively explore the mechanisms and associated features increasing the risk of young-onset CIS in individuals with heavy drinking, such as alcohol type, recent consumption prior to index stroke,

cumulative lifetime risk of alcohol consumption and effects on the coagulation system. Reducing heavy alcohol consumption remains one of the main targets of lifestyle interventions in young individuals to mitigate their risk of IS, including CIS.

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