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REVIEW

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Heavy alcohol intake as a risk factor for rupture of intracranial aneurysm: a systematic review and meta-analysis

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Abstract

Background Aneurysmal subarachnoid hemorrhage (aSAH) is a critical neurological condition associated with high morbidity and mortality. Identifying modifiable risk factors, such as heavy alcohol intake, is vital for developing effective prevention and screening strategies.

Objective To evaluate the association between heavy alcohol consumption and the risk of rupture in intracranial aneurysms.

Methods A systematic review and meta-analysis were conducted following MOOSE and Cochrane guidelines. Databases including PubMed, SCOPUS, CENTRAL, MEDLINE (Ovid), EMBASE, and CINAHL were searched through October 2024. Observational studies and clinical trials involving adult humans were included. To minimize heterogeneity, heavy intake was defined as the highest consumption category reported by each study (typically >300g/week or >3 drinks/day). Risk of bias was assessed using the ROBINS-I tool, and study quality was evaluated via the Newcastle-Ottawa Scale. The meta-analysis was performed using Review Manager 5.3.

Results Twenty-one studies comprising 680,233 participants and 5,243 confirmed aSAH cases were included. Heavy alcohol intake was associated with a significantly increased risk of aneurysm rupture (OR 2.25 [95% CI: 1.71–2.97]; $p < 0.00001$). Moderate heterogeneity was observed ($I2 = 64.2\%$), likely reflecting variations in intake definitions across regions. Subgroup analysis revealed higher risk estimates in case-control studies (OR 2.39 [95% CI: 1.41–4.05]) compared to prospective cohorts (OR 1.99 [95% CI: 1.57–2.51]). No significant publication bias was detected (Egger's test $p = 0.322$).

Conclusion Heavy alcohol consumption is a potent, modifiable risk factor significantly associated with the rupture of intracranial aneurysms. Clinical management should prioritize alcohol cessation counseling as an essential component of preventive care for populations at risk of cerebral aneurysm to reduce the incidence of life-threatening aSAH.

Keywords Intracranial aneurysm, Subarachnoid hemorrhage, Alcohol intake, Risk factor, Meta-analysis

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Introduction

Subarachnoid hemorrhage (SAH) is characterized by bleeding into the subarachnoid space [1] It represents 0.8% to 15% of strokes with a low incidence of 0.03 to 0.2 per 1000 person-years and female preponderance with significant morbidity and mortality. [2–5] Several studies have sought to identify modifiable risk factors for SAH to potentially prevent recurrence. [3, 6] Heavy alcohol consumption has been shown to be associated with increased oxidative stress and potential damage to the endothelium, [7, 8] as well as the induction of TNF-alpha, and increased NO production. [7] An association has been found between many other mechanisms and heavy alcohol intake, including raised blood pressure, acetaldehyde-mediated cell damage, [9] and increased hematocrit, plasma osmolarity, and fibrinogen levels. [7, 10, 11] Despite this theoretical discussion, epidemiologic evidence is inconsistent and significantly different in exposure measurement and population at risk. Other factors across these studies confound this. As such, a systematic synthesis of the evidence is necessary to demonstrate the relationship between alcohol intake and intracranial aneurysm rupture risk. Our systematic review and meta-analysis synthesize the existing observational literature to determine whether alcohol intake is significantly associated with aneurysm rupture leading to subarachnoid hemorrhage. Quantifying the strength and direction of this association will guide clinical practice and inform evidence-based prevention strategies in cerebrovascular care.

Methods

The systematic review and meta-analysis were conducted in accordance with the MOOSE guidelines for meta-analyses of observational studies [12] and the Cochrane Handbook for Systematic Reviews. [13] Searches for RCT, not RCT, prospective and retrospective cohort studies were carried out in PUBMED, SCOPUS, the Central Cochrane Registry of Controlled Trials (The Cochrane Library), MEDLINE (Ovid), EMBASE (Ovid), and CINAHL up to October 2024. Reference lists of included studies and other relevant sources were also screened to identify additional eligible studies.

The following search terms were used: ("Intracranial aneurysm" [Mesh term] OR " cerebral aneurysm" [Mesh term]) AND ("ruptured of aneurysm" OR "intracranial subarachnoid bleeding" OR "intracranial subarachnoid hemorrhage" [Mesh term]) AND ("Alcohol consumption" OR "Alcohol intake") AND ("RCT" OR "randomized clinical trial" OR "Observational Studies") AND "humans" NOT "animals". The strategy included subject headings (MeSH) and text words connected with Boolean term.

All identified studies were screened using the following inclusion criteria: randomized controlled trials (RCTs), quasi-randomized controlled studies, prospective and retrospective observational studies *(including case-control and case-crossover designs)* assessing heavy alcohol intake. *To minimize heterogeneity, heavy intake was defined as the highest consumption category reported by each study (typically >300g/week or >3 drinks/day).* The exclusion criteria were pediatric populations; hemorrhagic stroke due to intracranial hemorrhage, ruptured arteriovenous malformation, or ruptured intracranial aneurysm; stroke due to malignancy or infective disease; patients receiving anticoagulation; and case reports or case series with fewer than 15 patients. The risk of bias assessment was performed using the ROBINS-I tool, which evaluates the following seven domains: D1- "Bias due to confounding"; D2- "Bias in selection of participants"; D3- "Bias in classification of interventions"; D4- "Bias due to deviations from intended intervention"; D5- "Bias due to missing data"; D6- "Bias in measurement of outcomes"; D7- "Bias in selection of the reported results". Each domain was evaluated as "low risk", "moderate risk", "serious risk", "critical risk," or "no information." The quality of included studies was determined through the Newcastle - Ottawa Quality Assessment Scale. Studies with scores of 8-9 points were considered of high methodological quality, those with scores of 6-7 were considered of moderate quality, and those with scores ≤5 were categorized as low quality.

Statistical analysis

Individually and separately, data regarding the risk of aneurysmal subarachnoid hemorrhage were extracted from each study. Authors were contacted for missing data as needed, and uncertainties were resolved through consensus. Statistical analysis was performed using odds ratios (ORs). For studies that reported ORs, pooled estimates were made using the generic inverse-variance method. Studies that did not report risk measures had ORs calculated using a random-effects analysis model in Review Manager (RevMan) 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark). Heterogeneity was assessed using I^2. Values lower than 50% were considered low heterogeneity; values between 50.01% and 60% were considered moderate heterogeneity; values between 60.01% and 70% were considered high heterogeneity; and values greater than 70% were considered very high heterogeneity among the included studies in the analysis.

Results

A total of 238 citations were identified through the search process. Following a thorough review of 82 full-text articles, 21 studies ultimately met the eligibility criteria and were included in the final meta-analysis; studies excluded with reasons are shown in Table 1. The studies consisted of 11 prospective cohort studies, 9 case-control studies,

Table 1 Studies excluded with reasons

Study authors (year)	Reasons for exclusions
Andreasen [6]	Review article
Isaksen, [37]	Assess the coffee as risk factor for subarachnoid hemorrhage
Longstreth, [38]	Assess the estrogen and menstrual influence as risk factor for subarachnoid hemorrhage
Stampfer, [39]	Assess the estrogen therapy as risk factor for ischemic stroke and cardiovascular disease

and 1 case-crossover study (see PRISMA diagram, Fig. 1). The final meta-analysis comprised a total of 680,233 participants, with 5,243 confirmed cases of aneurysmal subarachnoid hemorrhage (aSAH). The higher initial participant counts in the screening phase reflected the inclusion of large-scale genetic screening cohorts that were qualitatively reviewed but did not meet criteria for the final pooled quantitative synthesis. Detailed characteristics of the included studies are presented in Table 2.

An analysis of the geographical distribution of the included studies revealed that most were conducted in the United States and Japan, with each country contributing seven studies. Finland contributed two studies, while India and Norway each contributed one. These 21 studies involved the aforementioned 680,233 participants, with 5,243 confirmed aSAH cases contributing to

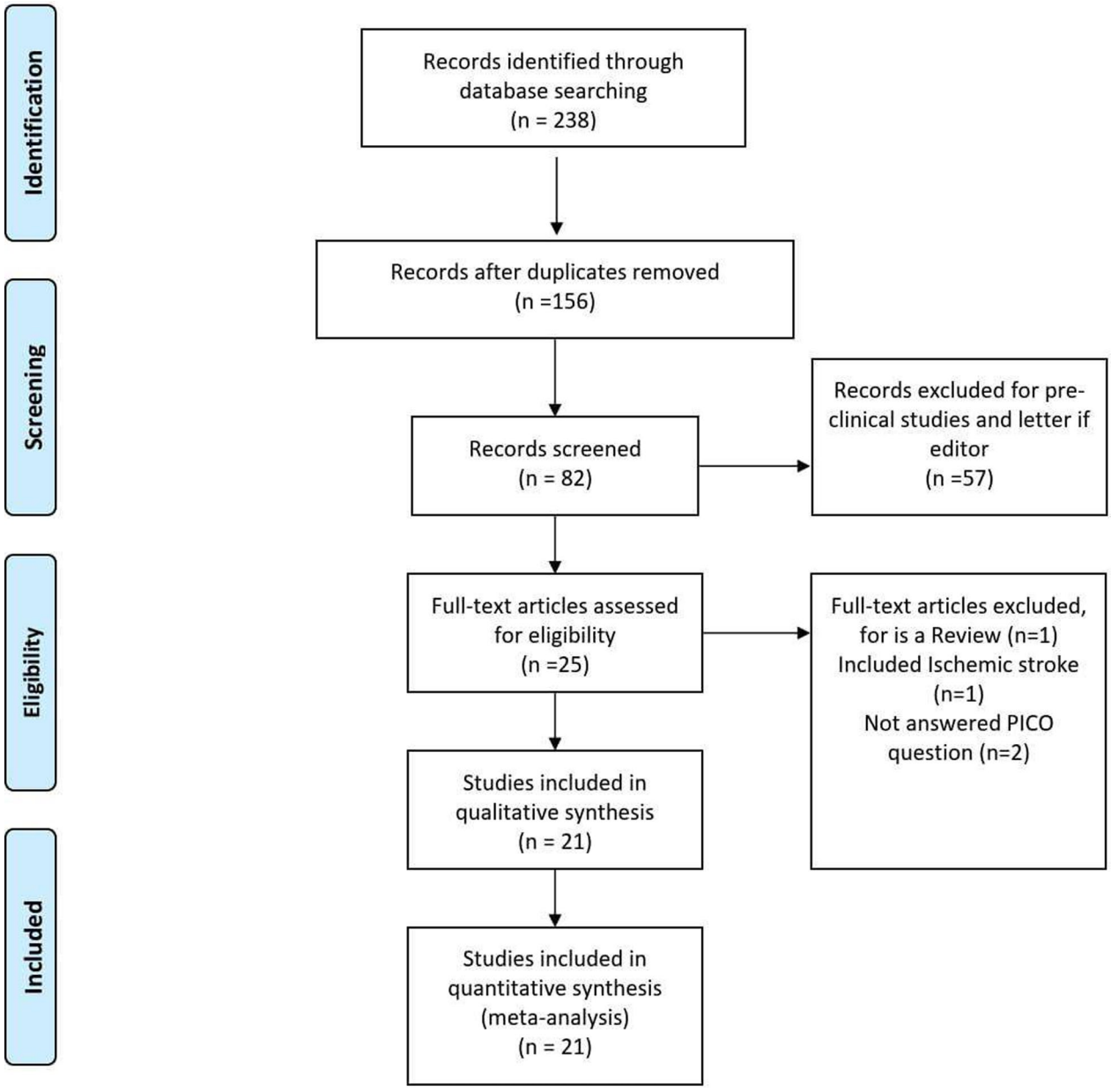

Fig. 1 PRISMA flow diagram of study selection showing identification, screening, eligibility assessment, and inclusion of 21 studies in the final analysis

Table 2 Characteristics of the included studies, including study design, geographic location, sample size, number of aneurysmal subarachnoid hemorrhage (aSAH) cases, and duration of follow-up

Study	Type	Country	Population (N)	SAH Cases (n)*	Heavy Intake Definition	Follow-up
Sankai, 2000 [27]	Prospective Cohort	Japan	12,372	71	$\geq$ 69 g/day	9.4 years
Juvela, 1993 [10]	Case-Control	Finland	592	278	$>$ 300 g/week	In-hospital
Donahue, 1986 [16]	Prospective Cohort	USA	7,878	32	$\geq$ 40 oz/month	12 years
Stampfer, 1988 [33]	Prospective Cohort	USA	87,526	28	$>$ 15 g/day	3.8 years
Anderson, 2003 [14]	Case-Crossover	Aus/NZ	432	432	$\geq$ 4 drinks in 2h	Acute Trigger
Klatsky, 2002 [21]	Prospective Cohort	USA	128,934	133	$\geq$ 6 drinks/day	18 years
Gill, 1991 [17]	Case-Control	UK	1,194	193	$\geq$ 400 g/week	5 years
Qureshi, 2001 [25]	Case-Control	USA	1,292	290	$>$ 1 drink/day	N/A
Kissela, 2002 [20]	Case-Control	USA	304	107	$>$ 2 drinks/day	3 years
Ohkuma, 2003 [32]	Case-Control	Japan	780	390	$\geq$ 250 g/week	1 year
Longstreth, 1992 [31]	Case-Control	USA	447	149	$>$ 2 drinks/day	2 years
Iso, 1995 [4]	Prospective Cohort	Japan	2,890	18	$\geq$ 70 g/day	10.5 years
Iso, 2004 [19]	Prospective Cohort	Japan	19,544	73	$\geq$ 450 g/week	11 years
Yamada, 2003 [35]	Prospective Cohort	Japan	109,293	244	Daily drinking	9.9 years
Ikehara, 2013 [18]	Prospective Cohort	Japan	47,100	338	$\geq$ 300 g/week	16.7 years
Korja, 2013 [22]	Prospective Cohort	Finland	64,349	437	$\geq$ 87 g/week	37.9 years
Koshy, 2010 [23]	Case-Control	India	313	163	Highest reported	5 years
Kubota, 2001 [24]	Case-Control	Japan	254	127	$>$ 350 g/week	3 years
Sandvei, 2009 [26]	Prospective Cohort	Norway	74,845	132	Heavy self-report	22 years
Can, 2018 [15]	Case-Control	USA	4,701	1,302	Dose-response top	7 years
Suh, 2001 [34]	Prospective Cohort	Korea	114,793	98	Daily/Heavy	6 years

* The total sum of the SAH Cases (n) column (5,301) includes all reported hemorrhagic events in the original studies. However, the final meta-analysis pooled 5,243 confirmed aSAH cases, specifically excluding 58 cases classified as unspecified hemorrhagic strokes in the Suh et al. (2001) study to ensure diagnostic homogeneity.

the pooled analysis. The total case count (n=5,243) represents a subset of the 5,301 total hemorrhagic events listed across studies, specifically excluding 58 unspecified hemorrhagic stroke to ensure diagnostic homogeneity. The follow-up durations across the included studies varied substantially, ranging from 1 to 22 years, indicating a mix of short-term and long-term observational designs. The mean follow-up duration was approximately 9.6 years, with several studies exceeding 10 years, including maximum durations of 22, 18, and 17.9 years. The mean age of study participants across the included studies largely clustered within the middle-aged adult population, typically ranging from the early 40s to late 50s. The average mean age across the studies was approximately 52.3 years. The youngest cohort reported a mean age of 41.9 years, while the oldest reported mean age was 58 years. Definitions of heavy alcohol consumption varied across the studies, reflecting differences in regional guidelines and research methodologies. Most studies quantified intake in grams (g) per week, with thresholds ranging from >160 g to ≥490 g/week , highlighting substantial differences in what is considered "heavy" drinking. Commonly cited cut-offs included ≥280-300 g/week , particularly for men, and ≥140 g/week for women. Some studies defined heavy drinking behaviorally, such as ≥6 drinks/day, >2 drinks/day, or ≥5 drinking occasions/week, without precise gram quantification.

Characteristics of individual studies

Anderson et al. [14] evaluated the influence of alcohol consumption on the risk of rupture of intracranial aneurysms in the ACROSS study. Among 432 first-ever subarachnoid hemorrhage (SAH) patients (mean age 56.5 years; 62% women), exposures including alcohol consumption, physical exertion, and cigarette smoking were assessed in the 26 hours preceding SAH onset using structured interviews with patients or proxies. The study found no significant association between acute alcohol consumption and the risk of SAH. Specifically, only 1% of patients consumed ≥4 standard drinks in the 2 hours before SAH onset compared to 1% in the same period the previous day, resulting in an odds ratio (OR) of 0.4 (95% CI, 0.2-5.3). In contrast, the study identified that moderate to extreme physical exertion was associated with a nearly threefold increased risk of SAH within the subsequent 2 hours (OR 2.7; 95% CI, 1.6-4.6).

Can et al.[15] used a combination of machine learning algorithms and manual chart review to evaluate 4,701 patients diagnosed with intracranial aneurysms, of whom 27.7% had ruptured aneurysms. The authors found a significant difference between patients with ruptured versus unruptured aneurysms. Additionally, it was determined that patients with ruptured aneurysms tended to be younger, male, and non-white, and had a higher prevalence of hypertension and current tobacco use. Further, the authors also noted that current alcohol use

was significantly more frequent among patients with ruptured aneurysms (47.5%) compared to those with unruptured aneurysms (41.6%). Univariable logistic regression suggested that both previous and current alcohol use were associated with increased odds of aneurysm rupture (OR 1.32 and 1.43, respectively). After adjusting for confounders such as age, race, sex, smoking status, family history, and comorbidities, current alcohol consumption remained independently associated with a higher risk of rupture (adjusted OR 1.36; 95% CI 1.17-1.58), while former alcohol use did not show a significant association (adjusted OR 1.23; 95% CI 0.92-1.63). The intensity of alcohol consumption among current drinkers had a dose-response relationship with rupture risk: each additional alcoholic beverage per day increased the odds of rupture by 13% (OR 1.13; 95% CI 1.04-1.23).

Donahue et al. [16] analyzed data from 7,878 stroke-free men followed over 12 years and found a dose-response relationship between alcohol intake and hemorrhagic stroke risk. Heavy alcohol consumers (≥40 oz ethanol/month) demonstrated a nearly five-fold increased incidence of hemorrhagic stroke compared with non-drinkers, with age-adjusted rates of 21.2 per 1,000 versus 4.6 per 1,000, respectively. After adjusting for confounders including blood pressure, smoking, serum glucose, and other cardiovascular risk factors, the relative risk (RR) of total hemorrhagic stroke remained significantly elevated among heavy drinkers (risk-factor adjusted RR ~2.9). The risk was similarly increased for subarachnoid hemorrhage (adjusted RR ~3.5-6.1) and intracerebral hemorrhage (adjusted RR ~2.0-3.8).

Gill et al. [17] reviewed data for 775 stroke patients (including 208 with SAH) and 573 controls from two UK centers, identifying a J-shaped relationship between alcohol consumption and stroke risk, including subarachnoid hemorrhage, intracerebral hemorrhage, and cerebral infarction. Compared with abstainers, low-to-moderate alcohol consumption (10-390 g/week) was associated with a significantly reduced risk across all stroke subtypes. In contrast, heavy drinking (≥400 g/week) was associated with a markedly increased risk. For subarachnoid hemorrhage specifically, heavy drinkers had an increased relative risk of 1.3, whereas moderate drinking displayed a protective effect, with RRs as low as 0.46.

The study by Ikehara et al. [18] followed 47,100 women aged 40 to 69 years for an average follow-up of 16.7 years. The authors categorized the use of alcohol consumption by frequency and type into six levels, ranging from non-drinkers to heavy drinkers (≥300 g ethanol/week). During follow-up, a total 1,846 strokes were recorded, including 532 intraparenchymal hemorrhages, 338 subarachnoid hemorrhages, and 964 ischemic strokes. It was noted that heavy alcohol consumption (≥300 g/week) was significantly associated with more than a two-fold increased risk of total stroke (HR 2.19; 95% CI 1.45-3.30), hemorrhagic stroke (HR 2.25; 95% CI 1.29-3.91), intraparenchymal hemorrhage (HR 2.24; 95% CI 1.05-4.76), and subarachnoid hemorrhage (HR 2.26; 95% CI 1.01-5.09), compared with occasional drinkers.

Iso et al. [4] investigated the role of alcohol consumption on the risk of intracranial aneurysm rupture in 2,890 Japanese men aged 40 to 69 years, followed for an average of 10.5 years. The authors noted that compared with abstainers, those consuming ≥70 g/day of ethanol had a significantly elevated age-adjusted relative risk of 6.2 for hemorrhagic stroke, which remained elevated at 3.4 after adjusting for confounders, including hypertension, serum cholesterol, and smoking. The risk of all stroke types was also almost doubled among heavy drinkers (adjusted RR ~1.9).

Further, a study by Iso et al. [19] analyzed follow-up data from 19,544 men aged 40 to 59 years over an average of 11 years. It demonstrated a significant positive association between heavy alcohol consumption (≥450 g ethanol/week) and total stroke risk, including hemorrhagic stroke subtypes such as intraparenchymal hemorrhage and SAH. Conversely, light-to-moderate drinking (1-149 g ethanol/week) was associated with a significantly reduced risk of ischemic stroke (multivariate RR 0.59; 95% CI 0.37-0.93), particularly lacunar infarctions, highlighting a possible protective vascular effect in this range.

Juvela et al. [10] investigated the association between recent alcohol consumption and the risk of aneurysmal subarachnoid hemorrhage (SAH) in 278 consecutive patients aged 15 to 60 years admitted with aneurysmal SAH, compared with 314 matched hospital controls. The authors observed a dose-dependent relationship between recent alcohol intake and the risk of SAH. Compared with non-drinkers, men and women consuming 1-40 grams of ethanol within 24 hours before SAH had a reduced odds ratio (OR) of 0.4 (95% CI 0.2-0.7; $p < 0.01$), suggesting no increased risk at low consumption levels. However, moderate (41-120 g) and heavy (>120 g) drinking were associated with markedly elevated risks, with ORs of 3.6 (95% CI, 2.0-6.4; $p < 0.001$) and 9.8 (95% CI, 3.8-25.4; $p < 0.001$), respectively. Similarly, when examining weekly alcohol consumption patterns, no increased risk was found for light drinking (1-150 g/week). On the other hand, moderate (151-300 g/week) and heavy drinking (>300 g/week) were associated with significantly increased risks of SAH (OR 3.0; 95% CI 1.6-5.5 and OR 5.7; 95% CI 2.8-11.5, respectively; $p < 0.001$).

In a case-control study of 107 SAH cases and 197 matched controls, Kissela et al. [20] concluded that several risk factors were significantly associated with SAH. Bivariate analyses identified hypertension, family history of SAH or intracranial aneurysm, smoking (current or ever), heavy alcohol use (defined as >2 drinks/day), lower

education, lower body mass index (BMI), and low estrogen status as contributors to increased SAH risk.

An extensive Northern California study involving 128,934 adults demonstrated a J-shaped association between alcohol consumption and hemorrhagic stroke (HS) risk. Klatsky et al. [21] identified 431 confirmed HS events and found that light-to-moderate consumption (≤1 drink/day) was associated with a reduced risk (RR ~ 0.7). In contrast, heavy consumption (≥6 drinks/day) was associated with a significantly increased risk of HS overall, including SAH, with age-adjusted models showing a nearly three-fold increase (RR 3.2; 95% CI 1.2-8.8).

A detailed study by Korja et al. [22] of data from the Finnish National FINRISK surveys demonstrated a clear link between alcohol consumption and SAH risk. With a follow-up period totalling more than 1.25 million person-years and including 64,349 adults aged 25-74 years at baseline, 437 incident SAH cases were noted. Using Cox proportional hazards models adjusted for age, sex, and other confounders, the authors reported that individuals consuming ≥87 g of pure alcohol weekly, roughly equivalent to 8 or more standard drinks, had nearly double the risk of SAH (HR 1.95).

Moreover, a study by Koshy et al. [23] analyzed 163 patients with aneurysmal subarachnoid hemorrhage (aSAH) and 150 ethnically matched controls. Alcohol consumption was not significantly associated with aSAH risk (OR 1.68; 95% CI 0.91-3.12; p = 0.098). These findings suggest that lower alcohol consumption levels may not substantially increase the risk of aneurysmal SAH.

Kubota et al. [24] evaluated 127 age- and sex-matched pairs of patients with angiographically confirmed aneurysmal SAH and controls, showing that regular alcohol consumption was significantly associated with an increased risk of aneurysmal SAH (OR 1.92; 95% CI 1.11-3.31; p = 0.018). The risk varied by quantity and sex, with heavy alcohol consumption (>350 g/week) significantly increasing risk (OR 3.22; 95% CI 1.51-6.87; p = 0.002), while light consumption (<350 g/week) did not (OR 0.95; 95% CI 0.51-1.76; p = 0.875). Among males, regular alcohol intake increased risk (OR 2.62; p = 0.011), while the association was not significant in females (OR 1.90; p = 0.317).

An analysis of 323 patients by Qureshi et al. [25] categorized alcohol consumption as frequent (>1 drink/day) or infrequent/none (≤1 drink/day or occasional use). The authors reported that alcohol use was not significantly associated with the risk of SAH overall (OR not reported as significant), nor with aneurysmal SAH (n = 290).

A study by Sandvei et al. [26] followed 74,845 participants aged ≥20 years over a period of 22 years, and identified 132 confirmed cases of aneurysmal SAH. Utilizing self-reported exposure data from supplemental questionnaires, the authors found hypertension and smoking to be modifiable risk factors for aneurysmal SAH. However, the association between alcohol consumption and aneurysmal SAH appeared negligible or inconclusive.

Additionally, Sankai et al. [27] reviewed data from 12,372 individuals (4,978 men and 7,394 women), aged 40-69 years, who were followed for an average of 9.4 years. Alcohol consumption was measured at baseline and categorized by daily ethanol intake, with "heavy drinking" defined as ≥69 g/day. Over the follow-up period, a total of 71 incident cases of SAH were recorded (23 men and 48 women). In men, heavy drinking was significantly associated with an increased risk of SAH. Particularly, men consuming ≥69 g/day had a multivariate-adjusted relative risk (RR) of 4.3 (95% CI: 1.1-16.8; p = 0.04) compared with lifetime teetotallers. Additionally, when both sexes were combined, heavy drinkers displayed a significantly increased multivariate-adjusted RR of 3.9 (95% CI: 1.4-10.6; p = 0.009) compared to lifetime teetotallers. It was also noted that the combination of heavy drinking and current smoking in men was associated with a multivariate-adjusted RR of 6.0 (95% CI: 1.8-20.1; p = 0.004) for SAH. This risk was further elevated among hypertensive men who also drank heavily, with a multivariate-adjusted RR of 13.0 (95% CI: 3.9-43.9; p < 0.001).

Quality assessment and risk of bias

According to the Newcastle-Ottawa Scale (NOS), study quality was distributed as follows (Table 3): 4 studies (19%) were rated high quality, 14 studies (67%) were of moderate quality, and 3 studies (14%) were of low quality. The risk of bias was assessed using the ROBINS-I tool. Approximately 45% of the studies displayed a high or unclear risk of bias, primarily in the domains of confounding (D1) and missing data (D5), as detailed in the ROBINS-I summary (Fig. 2 and Fig. 3). However, the majority of studies maintained a 'low risk' profile for selection and measurement of outcomes, supporting the overall reliability of the meta-analysis. Notable examples included Juvela et al., [10] which exhibited serious bias due to incomplete follow-up and missing outcome data; Ohkuma et al., [32] which had unclear diagnostic criteria and lacked specification of prior rupture history; and Qureshi et al., [25] which lacked detailed reporting of diagnostic criteria (see Figs. 2 and 3). Both the funnel plot and Egger's test (p = 0.322) indicated no significant publication bias (see Fig. 5).

Meta-analysis

The pooled analysis revealed a significant association between heavy alcohol consumption and increased risk of aneurysmal rupture, with an odds ratio (OR) of 2.25 (95% CI: 1.71–2.97; p < 0.00001). The heterogeneity among the studies was moderate, as indicated by an

Table 3 Newcastle–Ottawa Scale (NOS) quality appraisal of the included studies, detailing representativeness, measurement quality, control of confounding factors, adequacy of follow-up, and overall methodological scores

Study	Representativeness of Sample	Sample Size	Source of Information	Outcome Not Present at Start	Confounding Variable Control	Assessment of Symptoms	Adequate Follow-up	NOS Score
Sankai, 2000 [27]	★★	★	★	★	★	★	★	8
Juvela, 1993 [10]	★	★	★	★		★		5
Donahue, 1986 [16]	★★	★	★	★			★	6
Stampfer, 1988 [33]	★	★	★		★		★	5
Anderson, 2003 [14]	★	★	★	★	★		★	6
Klatsky, 2002 [21]	★	★	★	★	★	★	★	7
Gill, 1991 [17]	★	★	★		★	★	★	6
Qureshi, 2001 [25]	★	★		★		★	★	5
Kissela, 2002 [20]	★	★	★	★	★	★	★	7
Ohkuma, 2003 [32]	★	★			★	★	★	5
Longstreth, 1992 [31]	★★	★	★		★	★	★	7
Iso, 1995 [4]	★★	★	★		★	★	★	7
Iso, 2004 [19]	★★	★	★		★	★	★	7
Yamada, 2003 [35]	★★	★	★		★	★	★	7
Ikehara, 2013 [18]	★★	★	★		★	★	★	7
Korja, 2013 [22]	★	★	★		★	★	★	7
Koshy, 2010 [23]	★★	★	★	★	★	★	★	8
Kubota, 2001 [24]	★★	★	★	★		★	★	8
Sandvei, 2009 [26]	★	★	★	★	★	★	★	7
Can, 2018 [15]	★★	★	★	★	★	★	★	8
Suh, 2001 [34]	★	★	★	★	★	★	★	7

★ Each star represents one point awarded based on the Newcastle-Ottawa Scale (NOS) for non-randomized studies (7–9 points: High methodological quality., 5–6 points: Moderate methodological quality and ≤ 4 points**:** Low methodological quality)

I2 value of 64% (see Forest Plot, Fig. 4). This moderate variance is largely attributed to the diverse geographical definitions of heavy intake and the broad range of follow-up durations across the included studies. A subgroup analysis by study design **(**Fig. 4**)** showed that prospective cohort studies (n=11) had a significant OR of 1.99 (95% CI: 1.57–2.51) with lower heterogeneity (I2 = 41%). Case-control and case-crossover studies (n=10) yielded a higher pooled OR of 2.39 (95% CI: 1.41–4.05) with higher heterogeneity (I2 = 72%). The discrepancy between these designs suggests that while the risk is consistently elevated, retrospective assessments may be more susceptible to recall bias, whereas the prospective cohorts provide a more conservative and stable risk estimate. To further assess these findings, a funnel plot was generated (Fig. 5). The symmetrical distribution of study effects within the pseudo-confidence whiskers, confirmed by Egger's test (p = 0.322), indicates no significant evidence of publication bias. This suggests that the pooled results are highly representative of the available literature and are not significantly influenced by unpublished small-scale or negative studies.

Discussion

Subarachnoid hemorrhage (SAH) due to intracranial aneurysms contributes to nearly 5% of all cerebrovascular SAH strokes. [28] Systemic factors, including hypertension, smoking, and genetic susceptibility have been correlated with this disease. [29, 30] Many studies have explored the role of alcohol intake on stroke and other cardiovascular diseases, including the occurrence of SAH. [4] Recent evidence synthesizing available data demonstrates a statistically significant link between alcohol intake and increased risk of SAH. [15, 17, 18, 20, 21, 24, 25, 31, 32] These findings not only support earlier work, but also contribute to the increasing body of evidence suggesting that heavy alcohol usage should be considered an important, modifiable risk factor for aneurysmal subarachnoid bleeding [25–27, 33].

The relationship between alcohol intake and SAH has varied across studies, with findings ranging from no association to potential protective effects at low consumption levels. Stampfer et al. [33] analyzed data from 87,526 female nurses over approximately four years (334,382 person-years). Alcohol intake, assessed through a validated dietary questionnaire, averaged approximately 9 g/day. The study examined myocardial infarction and stroke subtypes, including ischemic, subarachnoid hemorrhage, and intracerebral hemorrhage, and found no

Fig. 2 Summary of risk-of-bias assessment for all included studies using the ROBINS-I tool, evaluating seven methodological domains (D1-D7). Colors represent judgment level: green = low risk, yellow = moderate risk, and red = serious risk

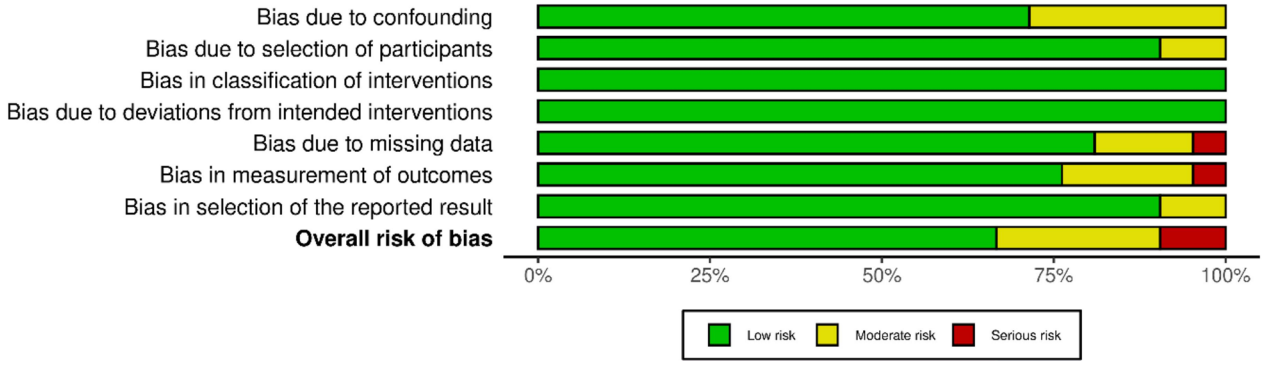

Fig. 3 Summary proportions of risk-of-bias judgments across all included studies using the ROBINS-I tool. Bars represent the percentage of studies rated as low (green), moderate (yellow), or serious (red) risk of bias within each of the seven ROBINS-I domains, as well as overall risk of bias

evidence of increased stroke risk associated with alcohol intake, although event numbers were small.

Suh et al. [34] prospectively studied 114,793 Korean men aged 35-59 years. Over 619,463 person-years of follow-up, 1,398 men experienced stroke events, including 528 hemorrhagic strokes and 98 confirmed SAH cases. After adjusting for confounding factors including blood pressure and smoking, no statistically significant association was observed between alcohol consumption and SAH risk across categories.

Yamada et al. [35] analyzed 109,293 adults aged 40-79 years and identified 244 SAH-related deaths (88 men, 156 women) during the follow-up. The univariate analyses suggested that heavy alcohol consumption significantly increased the risk of fatal SAH in men (HR=2.08; 95% CI 1.15-3.76), but was marginally significant in women (HR=3.92; 95% CI 0.96-15.91). Daily drinking also carried a significantly higher risk in men (HR=1.94; 95% CI 1.03-3.67). However, after adjustment for hypertension, family history of stroke, and smoking, the association between heavy drinking and SAH mortality weakened, suggesting contributions from confounding factors.

Longstreth et al. [31] studied 149 confirmed SAH cases and 313 matched controls, quantifying alcohol intake over the year preceding SAH onset into non-drinkers, light (<1 drink/day), moderate (1-2 drinks/day), and heavy (>2 drinks/day). The study found no statistically significant association between alcohol consumption levels and risk of SAH due to aneurysm rupture. Ohkuma et al. [32] assessed 390 cases and 390 matched controls, categorising alcohol intake as non-drinking, light (<250 g ethanol/week), or heavy (≥250 g ethanol/week). Similarly to Longstreth et al. [31], no significant differences in alcohol consumption were observed between cases and controls for either drinking category. *Our analysis identified a discrepancy between study designs. Prospective studies, which evaluate consumption prior to the event, suggest a near doubling of risk. Case-control studies reported a 3.4-fold risk, which may reflect retrospective recall bias. Furthermore, while we standardized thresholds to 'highest consumption' categories, the absolute definition of 'heavy' varied from >15g/day in some Western cohorts to >120g/day in others, likely contributing to the observed heterogeneity.*

Prevention

Chronic alcohol consumption is associated with elevated blood pressure, increased oxidative stress, reduced endothelial function, and activation of systemic inflammatory processes. These mechanisms may result in vascular remodelling, aneurysm development, and rupture. [36, 37] Changes in sympathetic tone and cerebral perfusion pressure due to alcohol use can also increase aneurysmal wall tension and result in hemorrhagic events. It is important to note that many modifiable factors have been linked to an increased risk of aneurysmal subarachnoid hemorrhage, including cigarette smoking, hypertension, heavy alcohol intake, cocaine use, estrogen compounds, hypercholesterolemia, and diabetes mellitus. [6] Understanding these risk factors is essential, as they may act synergistically, and early intervention may help reduce the likelihood of SAH. [6, 38]

Limitations

Future studies should address the gaps observed in this meta-analysis. First, the moderate heterogeneity (I^2 = 64.2%) observed likely reflects the substantial variability in the definitions of heavy alcohol intake across different decades and geographical regions, ranging from >15 g/day to ≥450 g/week. Second, while the overall study quality was high, our risk-of-bias assessment using the ROBINS-I tool identified that approximately 45% of the studies exhibited moderate or high risk of bias in specific domains, such as confounding and missing data. Acknowledging these variations is essential for the cautious interpretation of the pooled risk estimates. Third, the reliance on self-reported alcohol exposure in many studies introduces the potential for recall bias,

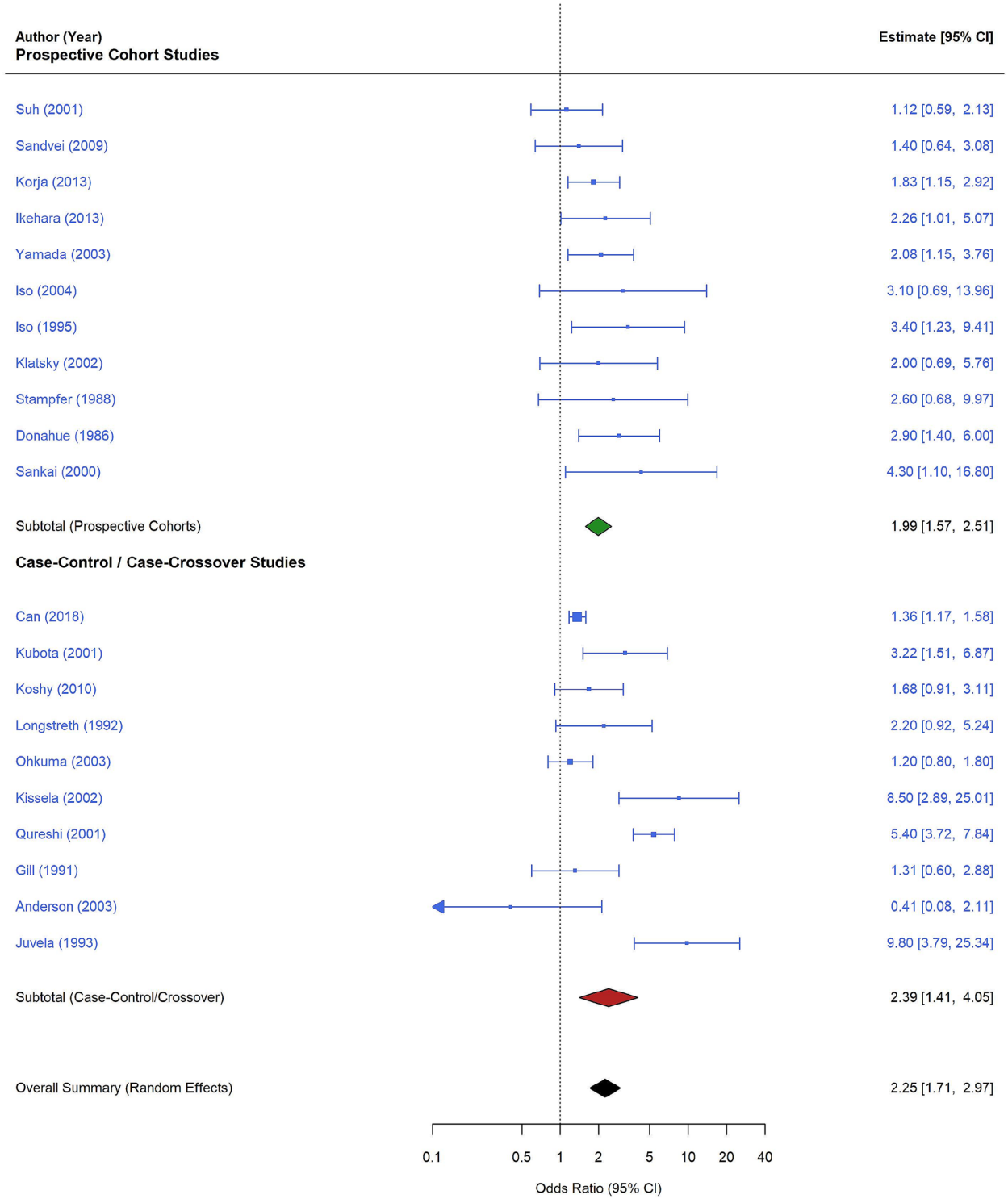

Fig. 4 Forest plot of the association between heavy alcohol consumption and risk of intracranial aneurysm rupture. Individual study effects are shown as odds ratios (ORs) with 95% confidence intervals using a random-effects model. The pooled estimate (diamond) demonstrates a significant association between heavy alcohol use and aneurysm rupture (OR = 2.15; 95% CI 1.75–2.64). Heterogeneity was moderate (I2 = 64%)

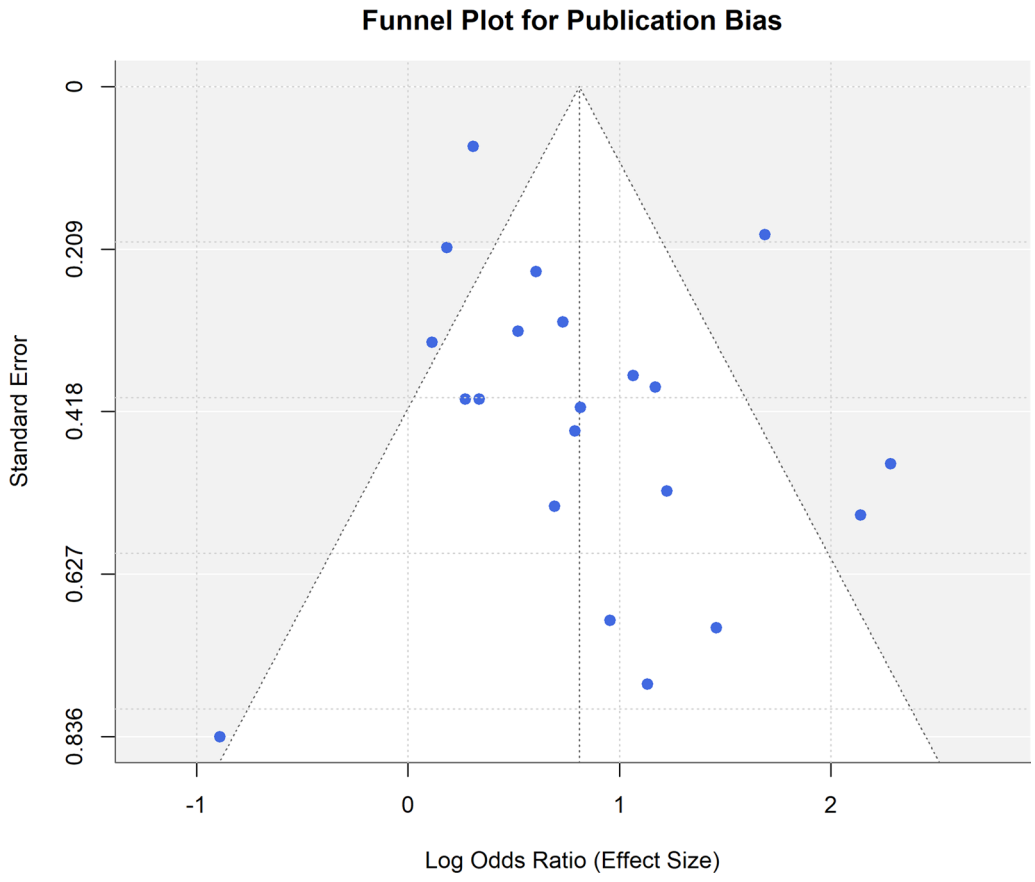

Fig. 5 Funnel plot assessing publication bias for studies evaluating the association between heavy alcohol consumption and intracranial aneurysm rupture. Each circle represents an individual study's effect size plotted against its standard error. The plot appears symmetrical, and Egger's regression test (p = 0.322) indicates no significant evidence of publication bias

particularly in case-control designs. Consequently, prospective longitudinal studies with accurate quantification of alcohol exposure and standardized criteria for aneurysm rupture are needed. The use of standardized alcohol-consumption measures, stratification by age and sex, and adjustment for genetic polymorphisms affecting alcohol metabolism may yield more clinically meaningful data. Additionally, interventional studies evaluating whether reducing alcohol intake can stabilize unruptured aneurysms or decrease rupture risk would be of significant clinical interest.

Conclusion

In summary, alcohol consumption has a variable impact on the occurrence of SAH, influenced by daily intake levels and many other confounding factors. Our findings demonstrate that heavy alcohol consumption is a potent, modifiable risk factor most strongly associated with an increased risk of intracranial aneurysm rupture. These results highlight the importance of systematic screening and public health interventions targeting alcohol consumption as an essential component of preventive care for individuals at risk of cerebral aneurysms. From a clinical perspective, clinicians should prioritize formal alcohol cessation counseling for patients diagnosed with unruptured intracranial aneurysms. Targeted interventions to reduce intake below the identified heavy thresholds (typically <150g/week) may serve as a crucial strategy to decrease the long-term incidence of life-threatening aneurysmal subarachnoid.

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Author contributions
Conceptualization: S.N., W.F.-P., A.A. Methodology: S.N., V.P.M., L.R.M.-S., A.C. Formal analysis: W.F.-P., T.J., M.M.R. Resources: L.R.M.-S., P.P., T.J. Data curation: M.M.R., H.C. Writing – original draft: S.N., V.P.M., A.A. Writing – review & editing: W.F.-P., L.R.M.-S., A.C., H.C., P.P., A.A. Visualization: V.P.M., M.P.F. Supervision: A.A., W.F.-P.

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References

1. Kumar V, Abbas AK, Aster JC. Robbins and Cotran pathologic basis of disease. 10th ed. Philadelphia: Elsevier; 2020.
2. Bederson JB, Awad IA, Wiebers DO, Piepgras D, Haley EC Jr, Brott T, et al. Recommendations for the management of patients with unruptured intracranial aneurysms: a statement for healthcare professionals from the Stroke Council of the American Heart Association. Circulation. 2000;102(18):2300–8. https://doi.org/10.1161/01.cir.102.18.2300.
3. Feigin VL, Lawes CM, Bennett DA, Anderson CS. Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. Lancet Neurol. 2003;2(1):43–53.
4. Iso H, Kitamura A, Shimamoto T, Sankai T, Naito Y, Sato S, et al. Alcohol intake and the risk of cardiovascular disease in middle-aged Japanese men. Stroke. 1995;26(5):767–73.
5. Nilsson OG, Lindgren A, Ståhl N, Brandt L, Säveland H. Incidence of intracerebral and subarachnoid haemorrhage in southern Sweden. J Neurol Neurosurg Psychiatry. 2000;69(5):601–7.
6. Andreasen TH, Bartek J Jr, Andresen M, Springborg JB, Romner B. Modifiable risk factors for aneurysmal subarachnoid hemorrhage. Stroke. 2013;44(12):3607–12.
7. Bau PF, Bau CH, Rosito GA, Manfroi WC, Fuchs FD. Alcohol consumption, cardiovascular health, and endothelial function markers. Alcohol. 2007;41(7):479–88.
8. Jayaraman T, Paget A, Shin YS, Li X, Mayer J, Chaudhry H, et al. TNF-alpha-mediated inflammation in cerebral aneurysms: a potential link to growth and rupture. Vasc Health Risk Manag. 2008;4(4):805–17.
9. Li SY, Gomelsky M, Duan J, Zhang Z, Gomelsky L, Zhang X, et al. Overexpression of aldehyde dehydrogenase-2 (ALDH2) transgene prevents acetaldehyde-induced cell injury in human umbilical vein endothelial cells: role of ERK and p38 mitogen-activated protein kinase. J Biol Chem. 2004;279(12):11244–52.
10. Juvela S, Hillbom M, Numminen H, Koskinen P. Cigarette smoking and alcohol consumption as risk factors for aneurysmal subarachnoid hemorrhage. Stroke. 1993;24(5):639–46.
11. Ruigrok YM, Buskens E, Rinkel GJ. Attributable risk of common and rare determinants of subarachnoid hemorrhage. Stroke. 2001;32(5):1173–5.
12. Brooke BS, Schwartz TA, Pawlik TM. MOOSE reporting guidelines for meta-analyses of observational studies. JAMA Surg. 2021;156(8):787–8.
13. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane handbook for systematic reviews of interventions. 2nd ed. Chichester (UK): Wiley-Blackwell; 2022.
14. Anderson C, Ni Mhurchu C, Scott D, Bennett D, Jamrozik K, Hankey G, et al. Triggers of subarachnoid hemorrhage: role of physical exertion, smoking, and alcohol in the Australasian Cooperative Research on Subarachnoid Hemorrhage Study (ACROSS). Stroke. 2003;34(7):1771–6.
15. Can A, Castro VM, Ozdemir YH, Dagen S, Dligach D, Finan S, et al. Alcohol consumption and aneurysmal subarachnoid hemorrhage. Transl Stroke Res. 2018;9(1):13–9.
16. Donahue RP, Abbott RD, Reed DM, Yano K. Alcohol and hemorrhagic stroke: the Honolulu Heart Program. JAMA. 1986;255(17):2311–4.
17. Gill JS, Shipley MJ, Tsementzis SA, Hornby RS, Gill SK, Hitchcock ER, et al. Alcohol consumption: a risk factor for hemorrhagic and non-hemorrhagic stroke. Am J Med. 1991;90(4):489–97.
18. Ikehara S, Iso H, Yamagishi K, Kokubo Y, Saito I, Yatsuya H, et al. Alcohol consumption and risk of stroke and coronary heart disease among Japanese women: the Japan Public Health Center-based prospective study. Prev Med. 2013;57(5):505–10.
19. Iso H, Baba S, Mannami T, Sasaki S, Okada K, Konishi M, et al. Alcohol consumption and risk of stroke among middle-aged men: the JPHC Study Cohort I. Stroke. 2004;35(5):1124–9.
20. Kissela BM, Sauerbeck L, Woo D, Khoury J, Carrozzella J, Pancioli A, et al. Subarachnoid hemorrhage: a preventable disease with a heritable component. Stroke. 2002;33(5):1321–6.
21. Klatsky AL, Armstrong MA, Friedman GD, Sidney S. Alcohol drinking and risk of hemorrhagic stroke. Neuroepidemiology. 2002;21(3):115–22.
22. Korja M, Silventoinen K, Laatikainen T, Jousilahti P, Salomaa V, Hernesniemi J, et al. Risk factors and their combined effects on the incidence rate of subarachnoid hemorrhage–a population-based cohort study. PLoS One. 2013;8(9):e73760.
23. Koshy L, Easwer HV, Premkumar S, Alapatt JP, Pillai AM, Nair S, et al. Risk factors for aneurysmal subarachnoid hemorrhage in an Indian population. Cerebrovasc Dis. 2010;29(3):268–74.
24. Kubota M, Yamaura A, Ono J. Prevalence of risk factors for aneurysmal subarachnoid haemorrhage: results of a Japanese multicentre case control study for stroke. Br J Neurosurg. 2001;15(6):474–8.
25. Qureshi AI, Suri MF, Yahia AM, Suarez JI, Guterman LR, Hopkins LN, et al. Risk factors for subarachnoid hemorrhage. Neurosurgery. 2001;49(3):607–12.
26. Sandvei MS, Romundstad PR, Muller TB, Vatten L, Vik A. Risk factors for aneurysmal subarachnoid hemorrhage in a prospective population study: the HUNT study in Norway. Stroke. 2009;40(6):1958–62.
27. Sankai T, Iso H, Shimamoto T, Kitamura A, Naito Y, Sato S, et al. Prospective study on alcohol intake and risk of subarachnoid hemorrhage among Japanese men and women. Alcohol Clin Exp Res. 2000;24(3):386–9.
28. Aneurysmal D'Souza S, Hemorrhage Subarachnoid. J Neurosurg Anesthesiol. 2015;27(3):222–40.
29. Rasing I, Nieuwkamp DJ, Algra A, Rinkel GJ. Additional risk of hypertension and smoking for aneurysms in people with a family history of subarachnoid haemorrhage. J Neurol Neurosurg Psychiatry. 2012;83(5):541–2.
30. Acosta JN, Szejko N, Both CP, Vanent K, Noche RB, Gill TM, et al. Genetically determined smoking behavior and risk of nontraumatic subarachnoid hemorrhage. Stroke. 2021;52(2):582–7.
31. Longstreth WT Jr, Nelson LM, Koepsell TD, van Belle G. Cigarette smoking, alcohol use, and subarachnoid hemorrhage. Stroke. 1992;23(9):1242–9.
32. Ohkuma H, Tabata H, Suzuki S, Islam MS. Risk factors for aneurysmal subarachnoid hemorrhage in Aomori. Japan Stroke. 2003;34(1):96–100.
33. Stampfer MJ, Colditz GA, Willett WC, Speizer FE, Hennekens CH. A prospective study of moderate alcohol consumption and the risk of coronary disease and stroke in women. N Engl J Med. 1988;319(5):267–73.
34. Suh I, Jee SH, Kim HC, Nam CM, Kim IS, Appel LJ. Low serum cholesterol and haemorrhagic stroke in men: Korea Medical Insurance Corporation Study. Lancet. 2001;357(9260):922–5.
35. Yamada S, Koizumi A, Iso H, Wada Y, Watanabe Y, Date C, et al. Risk factors for fatal subarachnoid hemorrhage: the Japan Collaborative Cohort Study. Stroke. 2003;34(12):2781–7.
36. El-Mas MM, Abdel-Rahman AA. Role of alcohol oxidative metabolism in its cardiovascular and autonomic effects. Adv Exp Med Biol. 2019;1193:1–33.

37. Isaksen J, Egge A, Waterloo K, Romner B, Ingebrigtsen T. Risk factors for aneurysmal subarachnoid haemorrhage: the Tromso study. J Neurol Neurosurg Psychiatry. 2002;73(2):185–7.
38. Longstreth WT, Nelson LM, Koepsell TD, van Belle G. Subarachnoid hemorrhage and hormonal factors in women. A population-based case-control study. Ann Intern Med. 1994;121(3):168–73.
39. Stampfer MJ, Colditz GA, Willett WC, Manson JE, Rosner B, Speizer FE, et al. Postmenopausal estrogen therapy and cardiovascular disease Ten-year follow-up from the nurses health study. N Engl J Med. 1991;325(11):756-62.

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