Alcohol consumption and risk of subarachnoid hemorrhage: A meta-analysis of 14 observational studies

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Abstract. The association between alcohol consumption and the risk of subarachnoid hemorrhage (SAH) is inconsistent. Thus, meta- and a dose-response analyses are presented with the purpose of assessing their associations. A systematic literature search was performed using Pubmed and Embase electronic databases for pertinent observational studies. Random-effects or fixed-effect models were employed to combine the estimates of the relative risks (RRs) with corresponding 95% confidence intervals (CIs). A dose-response pattern was conducted for further analysis. The current meta-analysis includes 14 observational studies reporting data on 483,553 individuals and 2,556 patients. The combined RRs of light alcohol consumption (<15 g/day) and moderate alcohol consumption (15-30 g/day) compared with teetotal individuals were 1.27 (95% CI: 0.95, 1.68) and 1.33 (95% CI: 0.84, 2.09), respectively, which indicated no significant association between light-to-moderate alcohol consumption and SAH. An increased risk of SAH was noted in heavy alcohol consumption (>30 g/day) when compared with no alcohol consumption, as demonstrated by a result of 1.78 (95% CI: 1.46, 2.17). Dose-response analysis showed evidence of a linear association (P=0.0125) between alcohol consumption and SAH. The risk of SAH increased by 12.1% when alcohol consumption was increased by 10 g/day. Therefore, heavy alcohol consumption was found to be associated with an increased risk of SAH. Furthermore, the association between SAH and alcohol consumption has clinical relevance with regard to risk factor modification and the primary and secondary prevention of SAH.

Introduction

Subarachnoid hemorrhage (SAH) is a destructive type of stroke, which contributes to ≥30% patients succumbing due to the original hemorrhage and rehemorrhage despite the development of novel treatment strategies (1-7). Although SAH is rare, it has a marked impact, particularly on young individuals, and poor outcomes (2,8,9). Therefore, it is vital to investigate the risk factors of SAH and attempt to prevent these with the aim of reducing the incidence of SAH. Alcohol consumption is common throughout the world and numerous observational studies have analyzed the role of alcoholic beverage intake and SAH, with some demonstrating alcohol as a risk factor or some presenting an unclear association (10-23).

In previous studies, alcohol intake and the risk of hemorrhagic stroke were investigated in the two meta-analyses, whereas intracerebral hemorrhage (ICH) and SAH were not classified in either of the studies (24,25). Furthermore, their investigative consequences primarily represented ICH, as the incidence of ICH was double that of SAH (26). The impacts of alcohol consumption on the incidence of SAH are inconclusive and limited. Another two systematic reviews presented the association between alcohol intake and the risk of SAH; however, the alcohol consumption level was inexact and a further association was not identified through dose-response analysis (27,28). Thus, the current meta-analysis, which included a dose-response analysis, was performed based on previous observational studies with the aim of identifying the specific association between various levels of alcohol consumption and the risk of SAH.

Materials and methods

Study selection. This meta-analysis was conducted on the basis of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement issued

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in 2009 (29). A systematic literature search of the Pubmed (http://www.ncbi.nlm.nih.gov/pubmed) and Embase (http://www.embase.com) electronic databases for pertinent studies published from their inception to 20 January 2016 was performed by two authors (Mr. Xiyang Yao and Dr Gang Chen) independently. The search strategy used terms as follows: 'Subarachnoid hemorrhage' AND ('alcohol' OR 'alcoholic beverages' OR 'ethanol' OR 'wine' OR 'liquor' OR 'spirits' OR 'beer'). No language restriction was set. In addition, a manual search of the probable missing publications of interest in our previous literature search was based on the reference lists of relevant studies.

Publications included in our meta-analysis complied with the following criteria: i) A study of the association between alcohol consumption and SAH; ii) case-control or cohort studies; iii) the effect estimate [relative risk (RR), hazard ratio (HR), odd ratio (OR)] and its corresponding 95% confidence intervals (CIs) were supplied (or enough data to calclulate them); iv) alcohol consumption was classified by quantity; v) the most informative study remained in the current meta-analysis if two or more published reports were based on the same research population.

Data abstraction and quality assessment. The following data were collected: First author's last name, published year, country, study design, assessment of alcohol consumption, sample size, female proportion, age at baseline, follow up duration (years), effect estimate and its 95% CI, and matched or adjusted factors. The Newcastle-Ottawa Scale (NOS) (30) was selected to assess the quality of the included studies. The NOS is composed of three subscales as follows: Selection, comparability and outcome. Furthermore, it includes a range from 0 to 9 stars, and a study was considered to be of high quality when it obtained ≥7 stars. Two authors (Mr. Xiyang Yao and Dr Gang Chen) gathered the data and evaluated the study quality separately. An additional author inspected and adjudicated the information according to the original studies.

Statistical analysis. RR with 95% CI measured the association between alcohol consumption and SAH. As the prevalence of SAH was relatively low, ORs and HRs were directly considered to be RRs (31). Adjusted RRs were employed in the meta-analysis and the crude data was used when the study didn't provide the adjusted data. The Q-statistic (P<0.1 was identified as statistically significant) and I^2 percentage (I^2: <50%, low heterogeneity; 50-75%, moderate heterogeneity; >75%, high heterogeneity) were used to evaluate the statistical heterogeneity between studies (32,33). The random-effects model was used when heterogeneity existed between studies and a fixed model was adopted otherwise (34). Subgroup analyses were performed according to gender, study design, geographic area, matched or adjusted status and study quality. Sensitivity analyses were conducted by omitting one study each time to evaluate the influence of the single study on the remaining studies. In addition, publication bias for the association between alcohol consumption and the risk of SAH was statistically assessed by Egger test (35) and Begg's test (36). P<0.05 was considered to indicate a statistically significant difference. When publication bias was apparent the 'trim and fill' method was used to modify it (37).

One drink was defined as 12.5 g, with 1 ml as 0.8 g and 1 oz as 28.35 g ethanol, and used grams of ethanol per day (g/day) as a standard measurement of alcohol consumption (38). The midpoint of each classification was taken as the quantity of alcohol consumption per day. When referring to the open-ended upper dose classification, it was counted as 1.2 times that of the lower bound for analyses (39). Non-drinkers were regarded as the reference category. Alcohol consumption was placed in three categories as follows: Light, <15 g/day; moderate, 15-30 g/day; and heavy, >30 g/day (25). When more than one category fell into one alcohol consumption level in certain studies, the RRs within a single category were combined for each study after which all studies were pooled (24). A dose-response analysis by generalized least squares regression models (40) was performed for further analysis and alcohol consumption (g/day) was considered as the explanatory variable. The potential curve linear correlation with alcohol consumption and SAH was evaluated using restricted cubic splines with three knots at percentiles 25, 50 and 75% of the distribution (41). The null hypothesis, where the coefficient of the second spline was equal to 0, was used to assess linearity or non-linearity according to a P-value (42). RRs with 95% CIs, distribution of cases and controls or person-years for at least three quantitative types of classifications have to be provided in initial studies. STATA 12.0 (StataCorp LP, College Station, TX, USA) was used to perform all statistical analyses.

Results

Literature search. Fig. 1 demonstrates the search flow. In total, 1,536 search records were yielded from the PubMed and Embase databases. There were 246 duplicates that were omitted, and 1,251 records were further removed after scanning the titles and abstracts, as these did not meet the inclusion criteria. The remaining 39 records were selected for full-text evaluation and 26 studies were excluded due to the following: Three studies were excluded because they were reviews (43-45). Two studies were excluded as they only investigated alcohol consumption within 24 h and one week before SAH, which was not representative of habitual alcohol consumption (46,47). Ten studies (48-57) that lacked sufficient data calculating RR estimates, and eight studies (58-65) where alcohol consumption had not been quantified were excluded. The remaining three studies reported on the same population (66-68). Furthermore, only one additional study of interest was identified during the manual search, which was then included (12). In total, 14 studies (10-23) were included in the current meta-analysis of which nine were cohort studies and five were case-control studies.

Study characteristics. The published period of the studies was from 1986 to 2013. Among the 14 studies, five were from the USA (10,11,14,20,22), one was from Britain (19), one was from Finland (18) and seven were from Japan (12,13,15-17,21,23). A total of 480,014 individuals were reported in the cohort studies and 35.2% were male. The follow-up period of the cohorts ranged from 3.8 to 17.9 years and the number of participants ranged from 2,890 to 128,934 in every cohort study. In addition, there were 1,182 cases and 2,357 controls from the five case-control studies. Seven of the studies achieved a rating of >6 stars and were, therefore, considered to be high quality.

Table I. Key characteristics of the included studies.

Author, year (Refs.)	Country	Subjects, n	Gender	Cases, n	Years of duration or study period	Exposure assessment	Adjusted or matched variables	NOS score
Cohort studies								
Donahue, 1986 (10)	USA	8006	M	32	12	IPI	a,b,f,g,i,j,k	6
Stampfer, 1988 (11)	USA	87526	F	28	3.8	SAQ	a	5
Iso, 1995 (12)	Japan	2890	M	18	10.5	IPI	a	6
Sankai, 2000 (13)	Japan	12372	M+F	71	9.4	IPI	a,b,d,f-i	8
Klatsky, 2002 (14)	USA	128934	M+F	133	7	SAQ	a-d,g,s	7
Yamada, 2003 (15)	Japan	109293	M+F	244	9.9	SAQ	a	7
Iso, 2004 (16)	Japan	19544	M	73	11	SAQ	None	7
Ikehara, 2013 (17)	Japan	47100	F	338	16.7	SAQ	a,d-f-i,m-o	7
Korja, 2013 (18)	Finland	64349	M+F	437	Median 17.9	SAQ	a,b	6
Case-control studies								
Gill, 1991 (19)	Britain	766	M+F	193	NR	SAQ	a-d,f,p-q,r	6
Longstreth, 1992 (20)	USA	447	M+F	149	1987-1989	IPI	a,b	7
Kubota, 2001 (21)	Japan	254	M+F	127	NR	SAQ	a,b	7
Qureshi, 2001 (22)	USA	1292	M+F	323	1990-1997	MR	a-c	4
Ohkuma, 2003 (23)	Japan	780	M+F	390	2000-2001	SAQ	None	5

Adjusted or matched variables were: (a) Age, (b) gender, (c) race, (d) cigarette smoking, (e) area, (f) hypertension, (g) BMI, (h) DM, (i) cholesterol, (j) uric acid and glucose concentrations, (k) hematocrit, (l) menopausal status, (m) mental stress, (n) facial redness after alcohol consumption, (o) sports at leisure time, (p) socioeconomic class, (q) treatment of hypertension, (r) medication, (s) education. M, male; F, female; NR, not reported; IPI, in-person interview; SAQ, self-administered questionnaire; MR, medical records; BMI, body mass index; DM, diabetes mellitus.
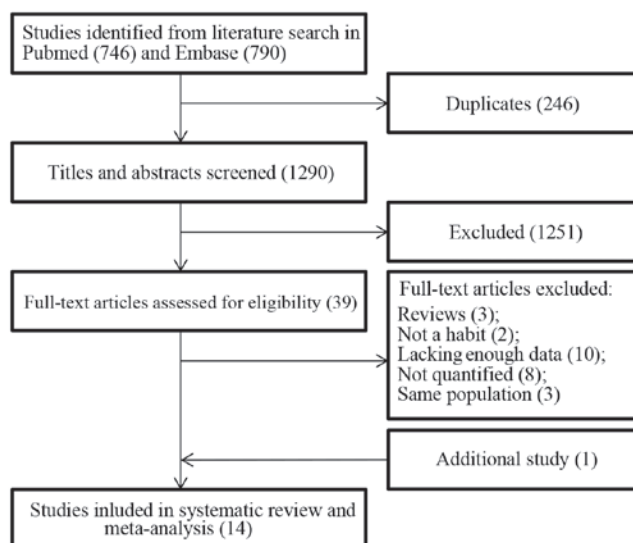

Figure 1. Flowchart of the search process.

Whereas, the remaining seven studies were considered to be low quality as a result of the star rating. Detailed characteristics are presented in Table I.

Alcohol consumption and risk of SAH. Figs. 2-4 demonstrate the outcomes from the random-effects model (light and moderate alcohol consumption) or fixed-effect model (heavy alcohol consumption) of pooled RRs for SAH. The combined RR of light alcohol consumption (<15 g/day) and moderate alcohol consumption (15-30 g/day) compared with no alcohol consumption were 1.27 (95% CI: 0.95, 1.68; $I^2=61.9\%$; P=0.005 for heterogeneity) and 1.33 (95% CI: 0.84, 2.09; $I^2=59.6\%$; P=0.022 for heterogeneity), respectively, which indicated no significant association between light or moderate alcohol consumption and SAH. Furthermore, the summary RR showed an increased risk of SAH when heavy alcohol consumption (>30 g/day) was compared with no alcohol consumption, with a pooled result of 1.78 (95% CI: 1.46, 2.17; $I^2=23.0\%$; P=0.218 for heterogeneity).

Stratified analyses. To minimize heterogeneity, stratified analyses were conducted between the included studies. The subgroups were generated in terms of pivotal study characteristics: Study design, gender, geographic area, type of SAH, study quality and adjustment status (smoking and blood pressure). The intact stratified results are presented in Table II.

For light alcohol consumption, total RRs of light alcohol consumption were not identified to be associated with the risk of SAH and had a moderate heterogeneity. However, if the study design was cohort, light alcohol consumption was observed to have an increased association with the risk of SAH and low heterogeneity, with RR of 1.53 (95% CI: 1.16, 2.02; $I^2=35.7\%$; P=0.156 for heterogeneity). Furthermore, the pooled RR of 1.46 (95% CI: 1.11, 1.93; $I^2=0\%$; P=0.468 for
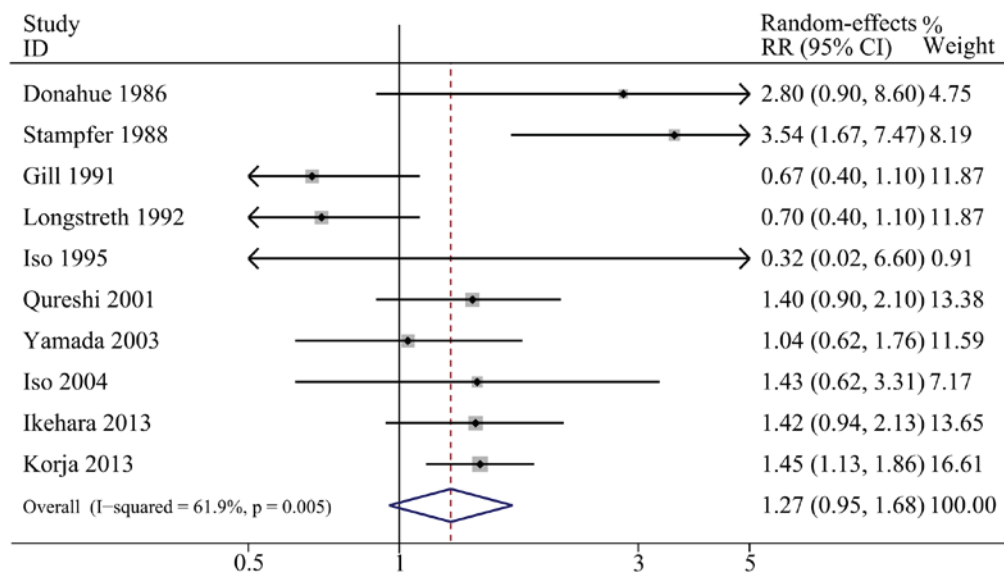
Figure 2. Forest plot of the association between light alcohol consumption and the risk of subarachnoid hemorrhage.
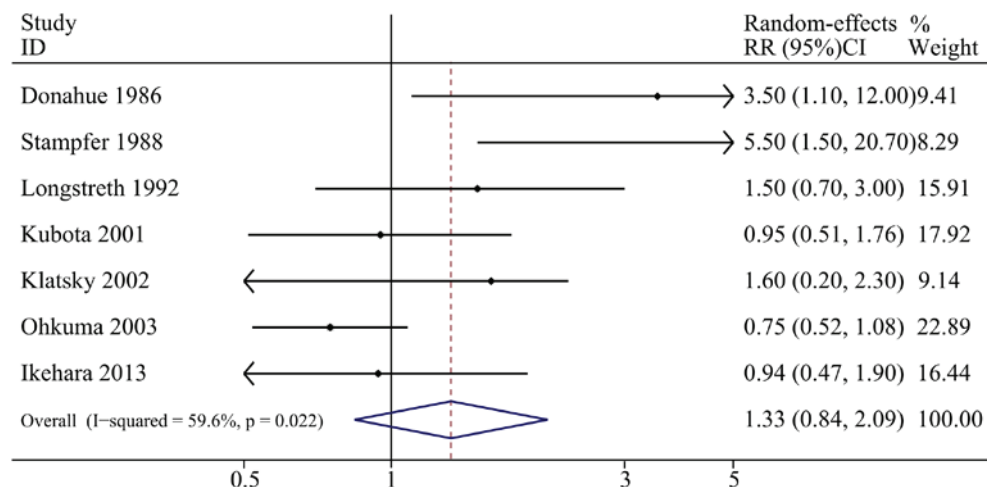
Figure 3. Forest plot of the association between moderate alcohol consumption and the risk of subarachnoid hemorrhage.
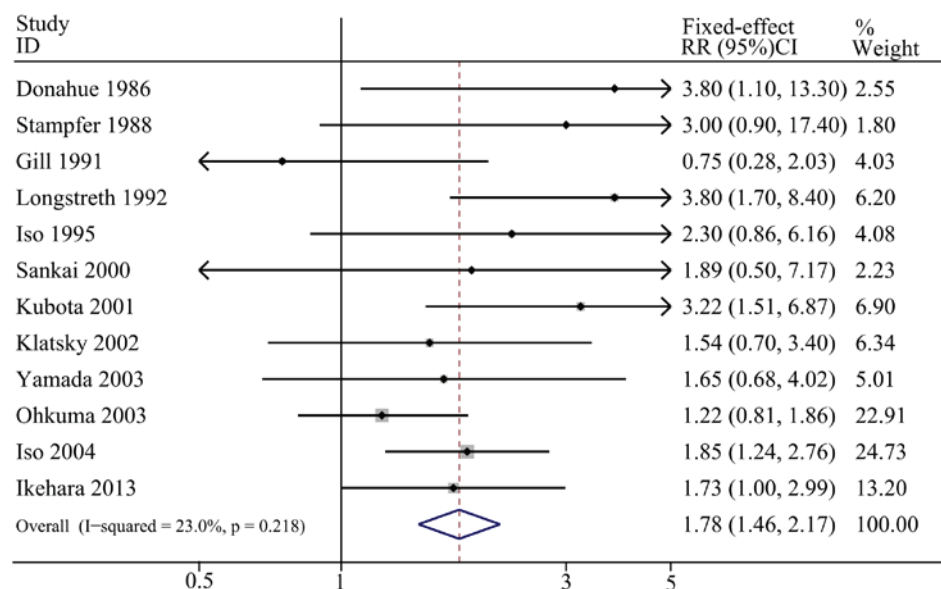
Figure 4. Forest plot of the association between heavy alcohol consumption and the risk of subarachnoid hemorrhage.

Table II. Summary RRs for alcohol consumption and SAH.

	Low alcohol consumption		Moderate alcohol consumption		Heavy low alcohol consumption	
	RR (95% CI)	P-value[a]	RR (95% CI)	P-value[a]	RR (95% CI)	P-value[a]
Total outcomes	1.27 (0.95,1.68)	0.10	1.33 (0.84,2.09)	0.23	1.78 (1.46,2.17)	<0.01
Study design						
Cohort	1.53 (1.16,2.02)	<0.01	2.08 (0.90,4.81)	0.09	1.88 (1.46,2.43)	<0.01
Case-control	0.88 (0.54,1.68)	0.63	1.33 (0.84,2.09)	0.68	1.64 (1.20,2.24)	<0.01
Gender						
Men	1.46 (1.11,1.93)	<0.01	3.5 (1.5,20.7)	0.04	1.77 (1.36,2.30)	<0.01
Women	1.33 (0.82,2.18)	0.25	2.41 (0.66,8.78)	0.18	1.27 (0.90,1.79)	0.18
Geographic area						
North America	1.63 (0.81,3.27)	0.17	2.16 (1.29,3.59)	<0.01	2.64 (1.63,4.28)	<0.01
Asia	1.26 (0.94,1.70)	0.13	0.82 (0.62,1.09)	0.17	1.71 (1.37,2.14)	<0.01
Europe	1.02 (0.48,2.16)	0.96	/	/	0.75 (0.28,2.02)	0.57
Type of SAH						
Total SAH	1.27 (0.95,1.68)	0.10	1.61 (1.07,2.44)	0.02	1.90 (1.50,2.41)	<0.01
aSAH	-	-	0.80 (0.58,1.09)	0.16	1.53 (1.06,2.20)	0.02
Study quality						
Low	1.49 (0.75,2.98)	0.26	2.19 (0.54,8.85)	0.27	1.41 (1.01,1.97)	0.04
High	1.20 (0.91,1.57)	0.20	1.12 (0.77,1.63)	0.55	2.02 (1.58,2.59)	0.02
Adjusted smoking						
Yes	1.23 (0.62,2.45)	0.56	1.54 (0.71,3.36)	0.27	1.62 (1.09,2.39)	0.04
No	1.31 (0.94,1.83)	0.12	1.25 (0.68,2.30)	0.47	2.02 (1.45,2.81)	<0.01
Adjusted blood pressure						
Yes	1.23 (0.62,2.45)	0.57	1.65 (0.46,5.92)	0.44	1.64 (0.94,2.87)	0.01
No	1.31 (0.94,1.83)	0.12	1.27 (0.74,2.18)	0.38	1.93 (1.44,2.58)	<0.01

[a]P<0.05 was considered to indicate a statistically significant difference. RR, relative risk; CI, confidence interval; SAH, subarachnoid hemorrhage; aSAH, aneurysmal subarachnoid hemorrhage.

heterogeneity) was statistically significant and there was no evidence of heterogeneity with regard to men and light alcohol consumption. No further statistically significant data was found in the geographic area, types of SAH, adjustment for smoking, adjustment for blood pressure and study quality.

For moderate alcohol consumption, no statistical significance was identified with the overall RRs of moderate alcohol consumption compared with the risk of SAH, and moderate heterogeneity was indicated. Notably, low heterogeneity was observed and an increased risk between moderate alcohol consumption and SAH was identified when the geographic area was North America and the type of SAH was total SAH. Furthermore, only one study mentioned the data regarding association with moderate alcohol consumption and the risk of SAH in a male population. No statistically significant information was found according to the results of the groups, such as study design, study quality and adjustments.

For heavy alcohol consumption, the RRs of women and adjustment for blood pressure along with heavy alcohol consumption did not show statistical significance with the risk of SAH, while other items indicated a statistically significant increased risk (Table II).

Sensitivity analyses and publication bias. The outcomes of sensitivity analyses were not identified to be significantly varied (data not shown). The Egger test (P=0.906) and Begg's test (P=0.719) indicated no evidence of publication bias for the association with light alcohol consumption and the risk of SAH. For heavy alcohol consumption, similar results were observed with the Egger test (P=0.235) and Begg's test (P=0.493). However, potential evidence of publication bias was found for SAH risk with moderate alcohol consumption according to the Egger test (P=0.004) and Begg's test (P=0.011). The adjusted result from the 'trim and fill' method for publication bias was 0.94 (95% CI: 0.57, 1.53), which did not change the former conclusions for SAH risk and moderate alcohol consumption. Fig. 5 demonstrates the funnel plot after applying the 'trim and fill' method.

Dose-response association. Seven studies were included in the dose-response analysis of alcohol consumption with SAH risk (10,11,14,16,17,19,20). A linear increase in SAH with increasing alcohol consumption (P=0.013) was observed after accessing dose-response patterns for alcohol consumption (g/day) for alcohol consumers vs. teetotal individuals (Fig. 6).
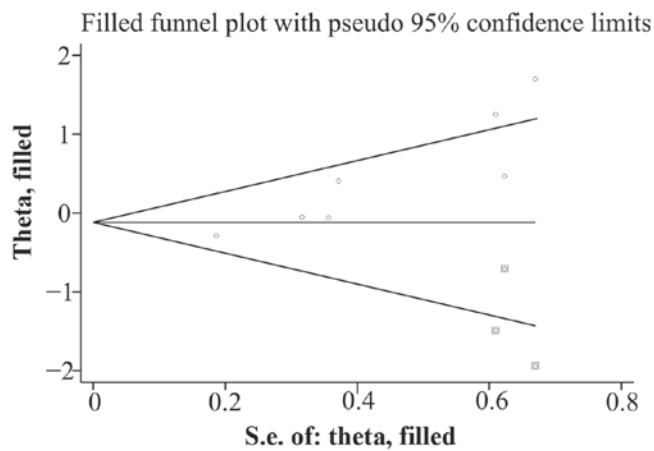
Figure 5. Presence of three potentially unreported studies were estimated using the 'trim and fill' method. S.e., standard error.

Figure 6. Dose-response correlation between subarachnoid hemorrhage risk and alcohol consumption. The solid line signifies the estimated relative risks and the dashed lines signify the 95% confidence intervals.

Furthermore, the risk increased by 12.1% for each additional 10 g/day of alcohol consumption.

Discussion

In the past several decades, the role of alcohol intake in the development of SAH has been increasingly recognized. Teunissen *et al* (27) conducted a systematic review about the risk factors for SAH, which five studies referring to alcohol intake and the risk of SAH. Alcohol abuse was identified to be a significant risk factor for SAH, with the results of drinking ≥21.4 g/day alcohol being RR=4.7 (95% CI: 2.1, 10.5) according to two longitudinal studies, and odds ratio (OR)=1.5 (95% CI: 1.1, 1.9) according to three case control studies. Subsequently, an updated systematic review of epidemiological studies was conducted by the same group, which demonstrated no different conclusions with the inclusion of extra studies (28). The current meta-analysis was based on observational studies that had quantified alcohol consumption with the aim of identifying probable correlations between alcohol consumption and the risks of SAH. The analysis included 483,553 individuals and 2,556 patients from nine

cohort and five case-control studies. The results indicated that there was no correlation between light or moderate alcohol consumption and the risk of SAH, while an increased risk of SAH was found to be associated with heavy alcohol consumption. The dose-response analysis evidenced a distinct linear association between alcohol consumption and SAH, which was consistent with the findings of Leppala *et al* (69). In addition, the dose-response analysis indicated an increased risk of 12.1% for every increase of 10 g/day alcohol when comparing drinkers to teetotal individuals.

The current findings confirmed the results from previous systematic reviews (27,28). Furthermore, the accuracy of the risk estimates was augmented with the accumulative data and stratified analyses were executed to evaluate the origin of heterogeneity (70), thereby advancing the clinical association of the present findings. Subgroup analysis indicated that light alcohol consumption was associated with an increase in SAH risk in cohort studies and men. Smoking was confirmed to be an independent risk factor for SAH (20,21,52,71,72) and men smoked more than women, which may be the explanation for the association between light alcohol consumption and the increased risk of SAH in men. Moderate alcohol consumption was associated with an increased risk of SAH in North American individuals; however, the explanation of this finding was unclear and requires additional investigation to be confirmed. Hypertension (73), reducing platelet aggregation (74) and enhancing fibrinolysis from endothelial cells (75) may be the reasons for the association between an increased risk of SAH and heavy alcohol consumption; although heavy alcohol consumption was not significantly associated with SAH in women. The potential reasons are as follows: i) Heavy drinkers were likely to be inclined to take part in the surveys as participants and less willing to complete repeat questionnaires in detail (11); ii) all volunteers in the study by Stampfer *et al* (11) were female nurses who may have had knowledge of the negative outcomes of drinking excessively, and therefore avoided heavy drinking (11); and iii) small population number (13,19). Notably, although hypertension has been consistently considered as the strongest predictor of SAH in previous studies (76-80), no correlation was found between heavy alcohol consumption and SAH risk in individuals from the included studies, which adjusted for blood pressure (10,13,17,19). However, the association between alcohol and stroke diminished markedly when adjusting for varying hypertension (3).

A notable strength of the present study is that it contains a broader individual population and has a longer follow-up when compared with previous studies. However, when interpreting the outcomes of the current meta-analysis, certain limitations should also be considered. First, the impact of potential confounding factors is a well-known issue resulting from the observational design of all of the included studies. In consideration of an osculating association between alcohol consumption and demographic, family history and lifestyle factors, the residual confounding factor should be categorized distinctly between these variables in future research. Second, information, select and recall bias usually lead to overestimating and underestimating the real associations in the observational studies. Furthermore, evidence of publication bias existed when pooling the results of correlation

with moderate alcohol consumption and the risk of SAH, although the conclusion remained unchanged following the 'trim and fill' method. Third, the strength of the correlation may have been weakened by misclassification bias. As the alcohol consumption assessment was based on self-reports and self-administered questionnaires, misclassification bias was inevitable. Finally, stratified analyses to examine the influence of different types of alcohol consumption on these correlations were conducted on account of the limited number of studies.

The present findings reveal various implications that are significant to public health. Individuals who reduce their alcohol consumption may also reduce their risk of SAH. Therefore, subjects who are alcohol drinkers should be encouraged to modify their habits to diminish the possibility of heavy alcohol consumption. Although small quantities of alcohol consumption are thought to reduce the risk of ischemic stroke (24,25), alcohol indeed promotes certain types of cancer, such as colorectal and gastric cancer (81,82) and, according to the present meta-analysis, increases the risk of SAH.

In conclusion, heavy alcohol consumption (>30 g/day) is associated with increased risk of SAH. The association between alcohol consumption and SAH has clinical implications for primary and secondary prevention of SAH. The implications of the findings require careful evaluation, as any suggestion regarding alcohol consumption must be tailored to the risks of each individual patient.

Acknowledgements

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