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Alcohol intake and the risk of glioma: a systematic review and updated meta-analysis of observational study

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Abstract

The association between alcohol intake and the risk of glioma has been widely studied, but these results have yielded conflicting findings. Therefore, we conducted this systematic review and updated meta-analysis to systematically evaluate the association between alcohol intake and the risk of glioma. A systematic literature search of relevant articles published in PubMed, Web of Science, CNKI and Wan fang databases up to December 2021 was conducted. Pooled estimated of relative risk (RR) and 95 % CI were calculated using fixed-effects models. A total of eight articles with three case–control studies involving 2706 glioma cases and 2 189 927 participants were included in this meta-analysis. A reduced risk of glioma was shown for the low–moderate alcohol drinking *v.* non-drinking (RR = 0·87; 95 % CI (0·78, 0·97); $P = 0·014$). In addition, there was no evidence of an increased risk of glioma in the heavy alcohol drinking compared with non-drinking (RR = 0·89; 95 % CI (0·67, 1·18); $P = 0·404$). The findings suggest an inverse association between low–moderate alcohol drinking and the risk of glioma, in the absence, however, of a dose–response relationship. More prospective studies are needed to provide further insight into the association between alcohol drinking and glioma risk.

Key words: **Alcohol intake: Glioma: Meta-analysis: Systematic review: Epidemiology**

Glioma is a devastating tumour of the central nervous system, accounting for approximately 80 % of adult malignant brain tumours[1]. It is reported that the global incidence rate of glioma is 3·7/100 000 for males and 2·6/100 000 for females[2]. Despite the low incidence rate, glioma is associated with high mortality and poor prognosis[3]. Indeed, apart from few established risk factors, such as exposure to ionising radiation, White race/ethnicity, little is known regarding the effect of modifiable risk factors (e.g. diet and alcohol intake) on glioma[4].Therefore, identifying the relationship of alcohol intake with glioma is valuable.

Over the past decades, alcohol intake has been recognised as an important risk factor for several types of cancer, including breast cancer[5], colocteral cancer[6] and liver cancer[7]. Alcohol is neurotoxic and can traverse the blood–brain barrier. A previous study has described the short- and long-term effects of excessive alcohol consumption on brain function and pathology[8]. To date, substantial epidemiological studies have explored the relationship between alcohol consumption and the risk of glioma[9–13]. But, results from these studies have been inconsistent. In the NIH-AARP Diet and Health Study, Braganza et al. found the significant inverse associations between alcohol and beer intake and glioma risk[9]. In addition, a recent report from three prospective cohort studies also found a significant inverse association between alcohol intake and glioma risk in both men and women[11]. However, in a hospital-based case–control study, Burch and his colleagues found that wine consumption was associated with an elevated risk of glioma[13]. Furthermore, a previous meta-analysis from nine observational studies has shown no material association between alcohol consumption and risk of glioma[14]. Therefore, to clarify the exact association between alcohol intake and glioma risk, we conducted this systematic review and updated meta-analysis to summarise the evidence from observational studies published up to December 2021.

Material and methods

This systematic review and meta-analysis has adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[15] and was written according to the Meta-analysis of Observational Studies in Epidemiology proposal[16].

Abbreviations: RR, relative risk.

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Literature search strategy

A comprehensive literature search was performed using the PubMed, Web of Science, CNKI and Wan Fang databases to identify relevant articles written in the English and Chinese languages published through December, 2021, with the following search terms: ('alcohol' OR 'ethanol' OR 'alcohol drinking' OR 'alcohol intake') AND ('glioma' OR 'gliblastoma' OR 'brain cancer' OR 'brain tumour'). The search was restricted to human studies. Moreover, we also reviewed the computer-retrieved studies for reference lists by hand-searching.

Studies included criteria

Two independent reviewers (Shu L and Jin FB) read the abstracts of articles retrieved in the initial search to identify human studies that examined the relationship between alcohol intake and the risk of glioma. Differences between the two independent reviewers were resolved by consensus and referred to the third reviewer if necessary. When all agreed, the full-text versions of articles were reviewed against inclusion and exclusion criteria for this meta-analysis. Studies were included if they met the follow criteria: (1) an original study reporting the association between alcohol intake and glioma risk; (2) used a case–control, nested case–control or cohort design; (3) estimates of relative risk (RR) (OR, hazard ratio and rate ratio) with corresponding 95 % CI were provided (or sufficient data to calculate them); and (4) if the data in original publication lacked sufficient detail, the corresponding author of the study was contacted for additional information by email. Studies were excluded if they met one of based on the follow criteria: written in a language other than English or Chinese; not performed on humans; reviews and letters; and studies with insufficient data. Finally, eight studies reported the association between alcohol intake and the risk of glioma.

Data extraction

Two reviewers (Shu L and Jin FB) independently extracted the following data from included studies: the first author's last name, publication year, geographic, study design, age for cases and participants, number of cases and controls or participants, type of controls, methods used for collection of data on exposure, exposure classification, confounders adjusted for, and the OR, RR or HR estimates with corresponding 95 % CI for the heavy drinking, low–moderate drinking *v.* non-drinking. Any discrepancies were resolved with a group discussion with a third investigator (Yu D).

Definition of 'high intake' and 'moderate intake'

The different forms of alcohol intake were converted into grams of ethanol per d (e.g. 1 drink = 12·5 g, 1 ml = 0·8 g, 1U = 8 g, 1 oz = 28·35 g of ethanol)[17]. Alcohol intake >25 g/d (or two drinks/d) for men or >12·5 g/d (or 1 drink/d) for women was defined as high intake of alcohol or heavy alcohol drinking; alcohol intake<12·5 g/d for men and <7·5 g/d for women was defined as low intake of alcohol or low alcohol drinking, and alcohol intake of >12·5/d and <25 g/d for men or >7·5 g/d and <12·5 g/d for women was defined as moderate alcohol drinking[18].

Assessment of heterogeneity

We performed the Cochran's Q test and I^2 statistic to test and quantify the heterogeneity among the included studies. A *P* value of Q test >0·10 indicated an absence of heterogeneity between included studies, and the fixed-effects model was used to calculated the pooled RR. If a *P* value of Q test ≤0·10 indicated a high degree of heterogeneity among studies, then the random-effects model (DerSimonnian and Laird method) was used[19].

Quality assessment

The Newcastle–Ottawa Quality Scale (NOS) was applied to assess the quality of the included studies in this meta-analysis[20]. This scale includes four points for selection, two points for comparability and three points for the assessment of outcomes. Finally, studies with a score of greater or equal to 7 were identified as high-quality studies[21]. Disagreements were resolved by discussion to reach a consensus.

Data synthesis and statistical analysis

To identify the relationship between alcohol intake and glioma risk, we used meta-analysis to summarise the risk estimate for the heavy drinking, low–moderate drinking *v.* non-drinking using OR, RR, and HR and corresponding 95 % CI for the included studies. Given the prevalence of glioma was relatively low, OR and HR were directly considered as RR[22]. Multivariable adjusted OR, HR and RR with corresponding 95 % CI from individual studies were combined to produce an overall RR. Publication bias was assessed by inspection of the funnel plot and by formal testing for 'funnel plot' asymmetry using Begg's test and Egger's test[23]. Moreover, sensitivity analysis was carried out to determine whether sex, study design, geographic area and study quality affected study conclusions. All statistical analyses were carried out using the STATA software, version 12 (Stata Corp.). Statistical tests were two-sided with *P* value<0·05 accepted as statistically significant.

Results

Overview of included studies for the systematic review

An electronic literature search in PubMed, Web of Science, CKNI and Wan fang database identified 401 studies, 393 of which were excluded based on the reasons listed in Fig. 1. Eight articles[9–12,24–27] met the inclusion criteria and were included in this meta-analysis, including five cohort studies[9,11,12,25,26] and three case–control studies[10,24,27].The characteristics of the included studies were summarised in Table 1.

Alcohol drinking

The heavy alcohol drinking was characterised by high intakes of alcohol-containing beers, wines and spirits. Pooled results form six articles (including eight original studies) identified a heavy

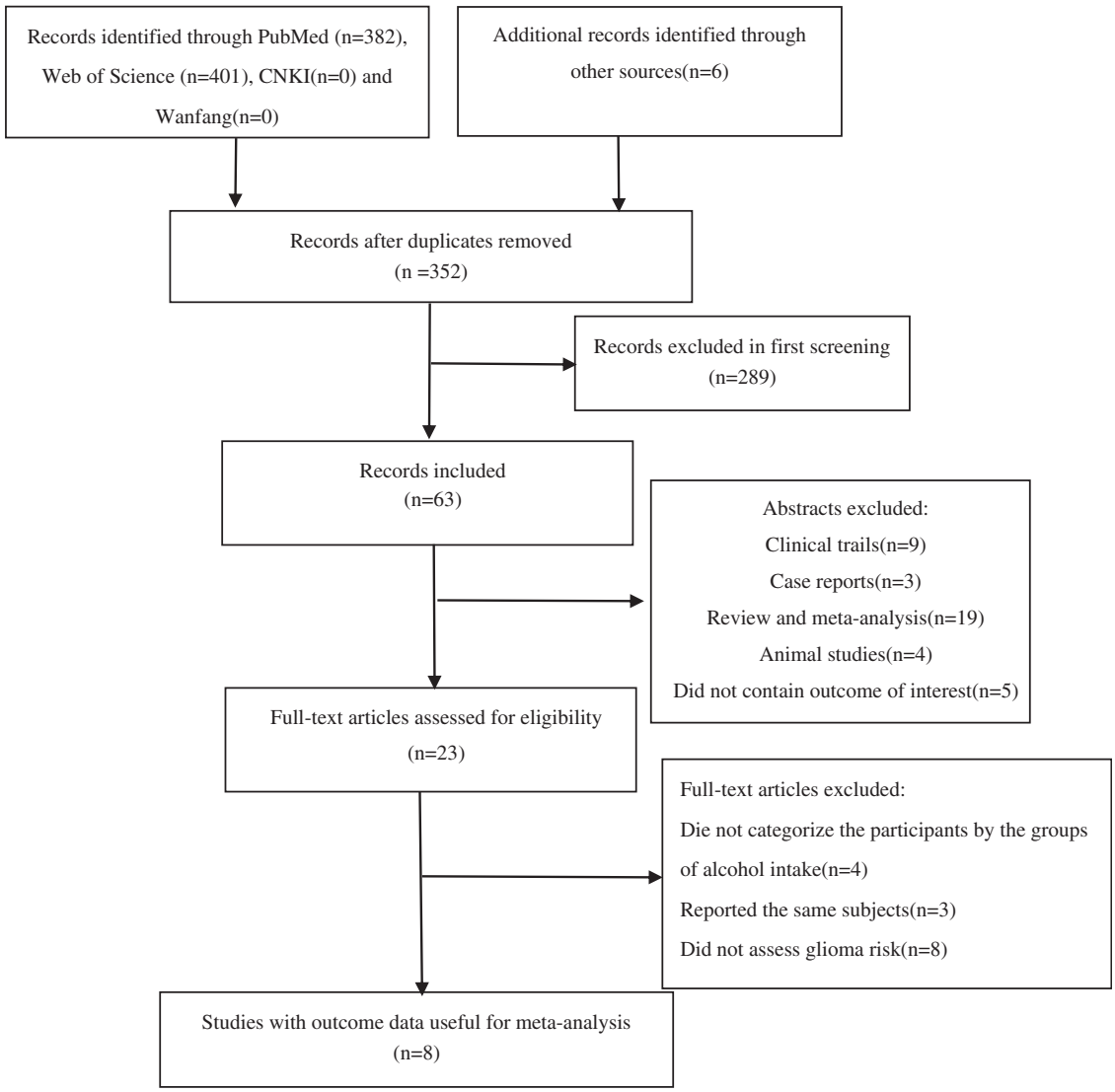

Fig. 1. Flow chart of article screening and selection process.

alcohol drinking (Fig. 2). Fig. 2 showed no evidence of an increased risk of glioma in the heavy alcohol drinking *v.* non-drinking (RR = 0·89; 95 % CI (0·67, 1·18); $P = 0·404$). Data from these studies were assessed using random-effects model, and there was significant heterogeneity ($I^2 = 43·7$ %, $P = 0·087$). Eight articles reporting eleven original studies identified a low–moderate alcohol drinking in this meta-analysis (Fig. 3). There was evidence of a reduced risk of glioma in the low–moderate alcohol drinking compared with non-drinking (RR = 0·87; 95 % CI (0·78, 0·97); $P = 0·014$). A fixed-effects model was used to assess the data, and there was no evidence of heterogeneity ($I^2 = 0·0$ %, $P = 0·656$).

Publication bias

Inspection of funnel plots did not reveal evidence of asymmetry (Fig. 4 and 5). Egger's test for publication bias was not statistically significant (heavy alcohol drinking *v.* non-drinking: $P = 0·536$; low–moderate alcohol drinking *v.* non-drinking: $P = 0·458$).

Quality assessment

The quality of included studies using Newcastle–Ottawa criteria is detailed in Appendix 1. When included studies received a score of 6 or higher, they would be deemed to be of relatively higher quality[9–12,23–26].

Sensitivity analysis

The sensitivity analysis revealed that differences in age, sex, ethnicity and study design had an effect on the relationship between alcohol intake and glioma risk. When moderate alcohol drinking was compared with non-drinking, the alcohol intake/glioma association was stronger when subjects were women, White and more than 50 years old, and study design was cohort. As these variables have a strong effect on relationship between alcohol intake and glioma risk, their differences may partially explain the heterogeneity between studies (Table 2).

Table 1. Characteristics of studies on alcohol intake and risk of glioma (–2021)
(Risk ratio, hazard ratio, odd ratio and 95 % confidence intervals)

First author, publication year	Country	Study design	No. of cases and controls/cohort	Age	Duration of follow-up	Information on alcohol drinking	RR/HR/OR	95 % CI	Adjustment or matched for
Branganza *et al.* 2014[9]	USA	Cohort	477 095	50–71 years	10·5 years	Alcohol	0·65 and 0·96 for heavy drinking in men and women, respectively; 0·92 and 0·79 for low–moderate drinking in men and women, respectively	0·47, 0·90 0·63, 1·48 0·69, 1·24 0·54, 1·16	Education, marital status and race/ethnicity.
Hurley *et al.* 1996[10]	Australia	Case–control	416 cases and 422 controls	20–70 years	–	Alcohol consumption	1·36 and 0·93 for heavy drinking in men and women, respectively; 1·30 and 0·55 for low–moderate drinking in men and women, respectively	0·73, 2·51 0·38, 2·25 0·66, 2·54 0·30, 0·99	Age and reference rate
Cote *et al.* 2021[11]	USA	Cohort	237 505	25–75 years	26·2 years	Total alcohol	0·62 for heavy drinking and 0·9 for low–moderate drinking in women; 0·57 for low–moderate drinking in men	0·39, 0·97 0·62, 1·30 0·36, 0·89	Age (months), smoking status (never *v.* past *v.* current), calendar year, BMI (< 25 kg/m^2 *v.* ≥ 25–< 30 kg/m^2 *v.* ≥ 30 kg/m^2) and total energetic intake (quintiles)
Baglietto *et al.* 2011[12]	Australia	Cohort	39 766	27–81 years	An average of 15 years	Total alcohol intake	2·54 for heavy drinking; 1·07 for low–moderate drinking	0·92, 7·01 0·55, 2·10	Sex, country of birth, total energy intake from diet, level of education and coffee consumption
Hu *et al.* 1999[24]	China	Case–control	129 cases (73 gliomas and 56 meningiomas) and 256 controls	20–74 years	–	Total alcohol	3·22 for heavy drinking; 0·80 for low–moderate drinking	1·5, 1·7 0·3, 2·2	Income, education, cigarette smoking, selected occupational exposures and total energy intake
Efird *et al.* 2004[25]	USA	Cohort	133 811	≥25 y	21 years	Alcohol	0·4 for heavy drinking; 0·90 for low–moderate drinking	0·1, 2·8 0·6, 1·4	Cigarettes, cigars, pipes, sex, race, education and coffee.
Benson *et al* 2008[26]	UK	Cohort	1·3 million	Middle-aged	5·9 years	Alcohol intake	1·11 for low–moderate drinking	0·92, 1·35	Height, BMI, smoking status, socio-economic status, age at first birth, strenuous exercise, parity and oral contraceptive use
Ryan *et al.* 1992[27]	Australia	Case–control	110 cases and 417 controls	25–74 years	–	Alcohol	1·0 for heavy drinking; 0·86 for low–moderate drinking	0·53, 1·91 0·47, 1·60	Age, sex and subject's own smoking history

Branganza 1, Hurley 1, cote 1, *et al.* represent the data for men. Branganza 2, Hurley 2, cote 2, *et al.* represent the data for women.

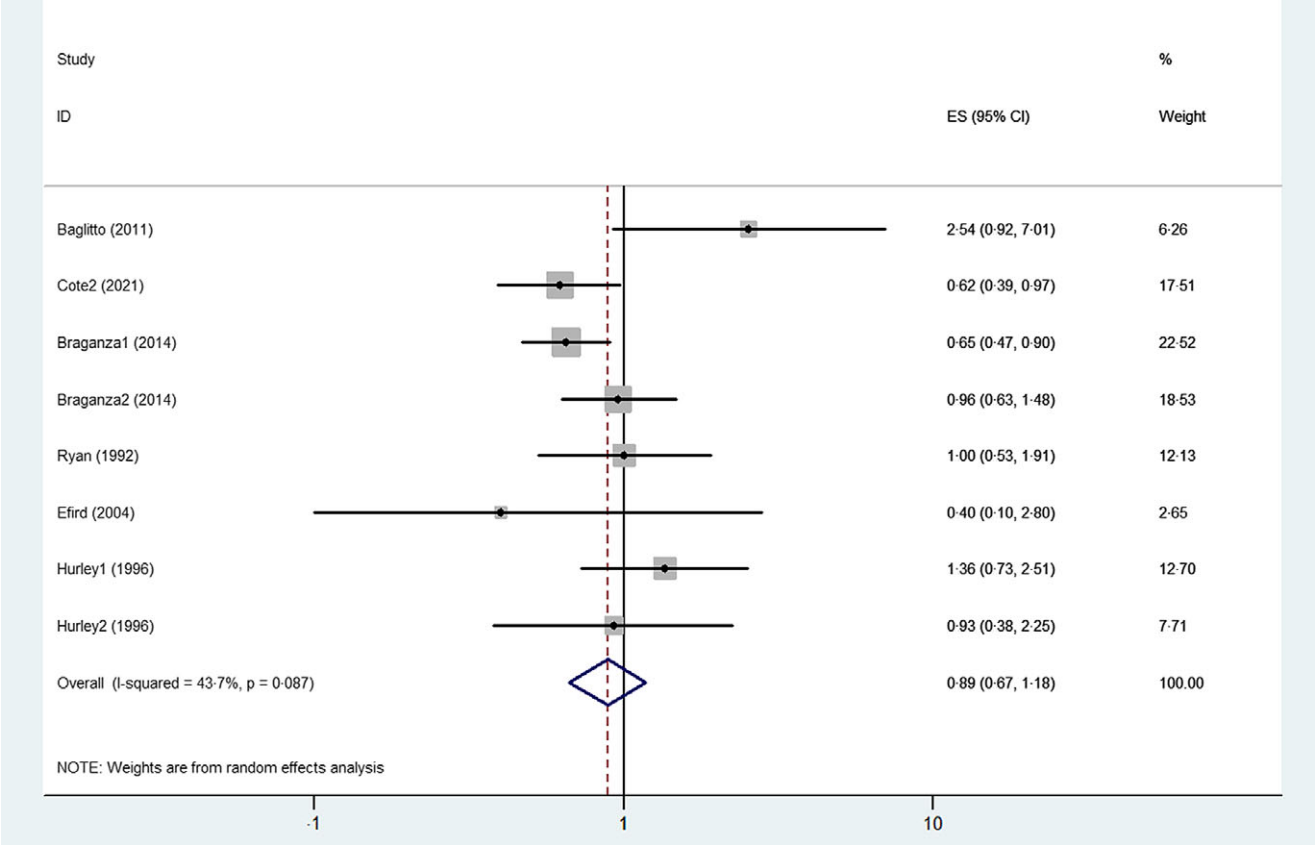

Fig. 2. Forest plots for RR of heavy alcohol drinking *v.* non-drinking. RR, relative risk.

Discussion

Existing evidence on the role of alcohol intake and the incidence of glioma is limited and inconsistent. To the best of our knowledge, this is the latest systematic review and meta-analysis on the effect of alcohol intake on glioma. In this study, we found a significant inverse association between low–moderate alcohol drinking and the risk of glioma. Meanwhile, no significant association between heavy alcohol drinking and the risk of glioma was observed. Data from eight articles involving 2706 glioma cases and 2 189 927 participants were included in this meta-analysis. Our findings provide further evidence on the role of alcohol intake and the risk of glioma, though the lack of a dose–response relationship suggests caution in the interpretation of results.

In our analyses, the significant inverse association was identified between low–moderate alcohol drinking and the risk of glioma. Our findings are inconsistent with a previous meta-analysis of alcohol consumption and the risk of glioma[14]. Qi *et al.* reported no material association between alcohol consumption and risk of glioma (total alcohol drinks *v.* non-drinks: RR = 0·96, 95 % CI (0·89, 1·04))[14]. In their meta-analysis, the main analysis is 'ever and alcohol drinkers *v.* nondrinkers'. Qi and colleagues did not analyse the relationship between different levels of alcohol consumption and the risk of glioma. Thus, a lack of consideration for the association between different drinking group and glioma could contribute somewhat the variance in results. In a comprehensive meta-analysis of alcohol consumption and risk of brain tumours, Galeone and colleagues also found that alcohol drinking did not appear to be associated with adult brain cancer[17]. The difference to our study is that Galeone et al. did not analyse glioma or glioblastom separately from other brain tumours. This analysis of combination of glioma and other brain tumours could make these findings more confounding. Also, inclusion of eight articles reporting eleven original studies with a larger sample size might explain the modest stronger association observed in our meta-analysis. In contrast, a more recent report from three prospective cohort studies found a significant inverse association between alcohol intake and glioma risk in both men and women[11]. Cote et al. estimated HR of glioma and 95 % CI by category of alcohol intake and adjusted the covariates including BMI, smoking status and total energetic intake. In the NIH-AARP Diet and Health Study, an analysis including 704 glioma cases also identified significant inverse, dose-dependent associations between alcohol and beer intake and risk of glioma, but no associations for wine or liquor[9]. In short, the evidence linking alcohol consumption with glioma is inconsistent. Although ethanol has been classified as carcinogenic to humans by the International Agency for Research on Cancer (IARC)[28], there are several plausible explanations for this favourable effect of low–moderate alcohol drinking on glioma. First, xanthohumol, a flavonoid present in beer, has exhibited its anticancer properties via inhibition of various

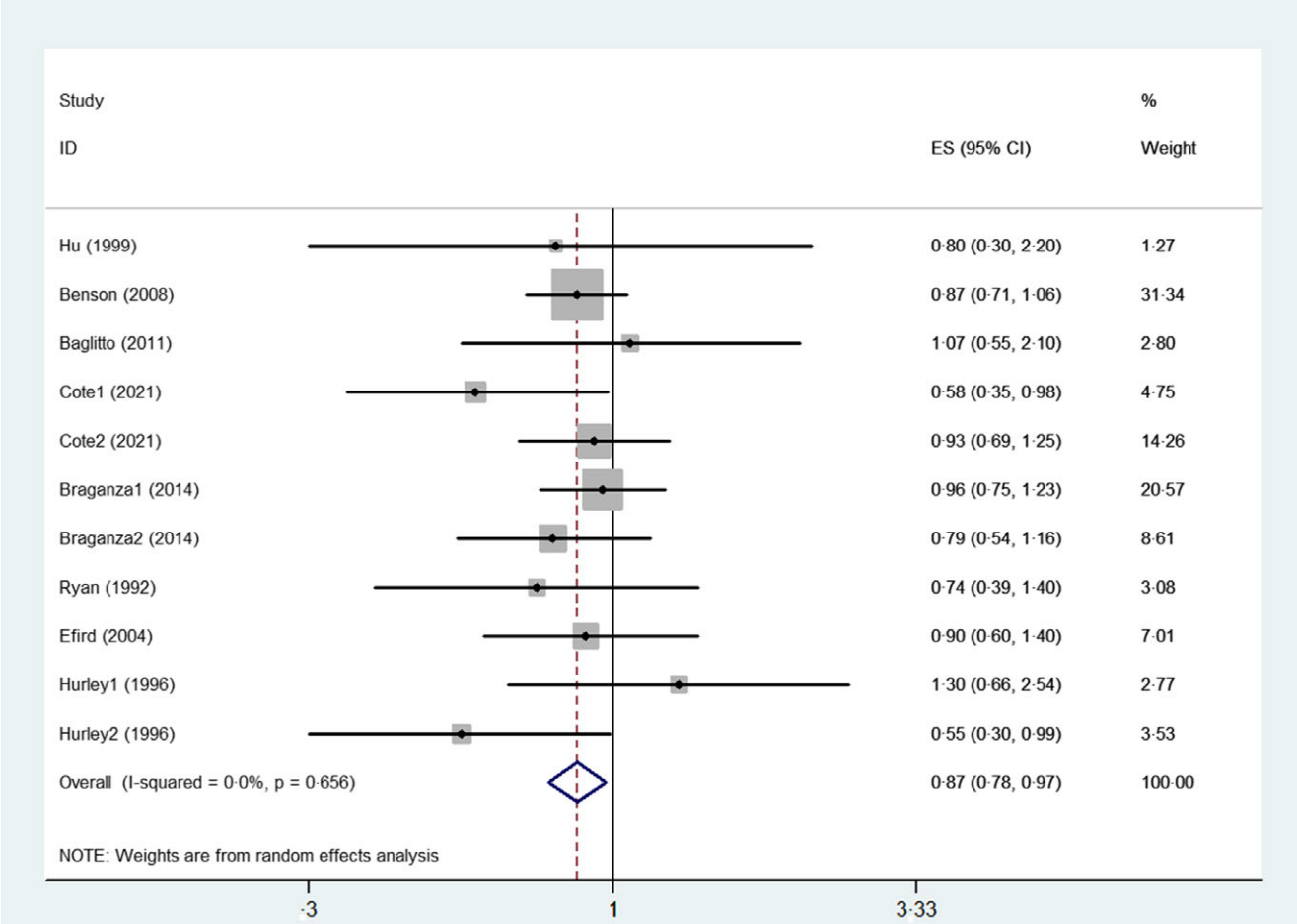

Fig. 3. Forest plots for RR of light–moderate alcohol drinking *v.* non-drinking. RR, RR, relative risk.

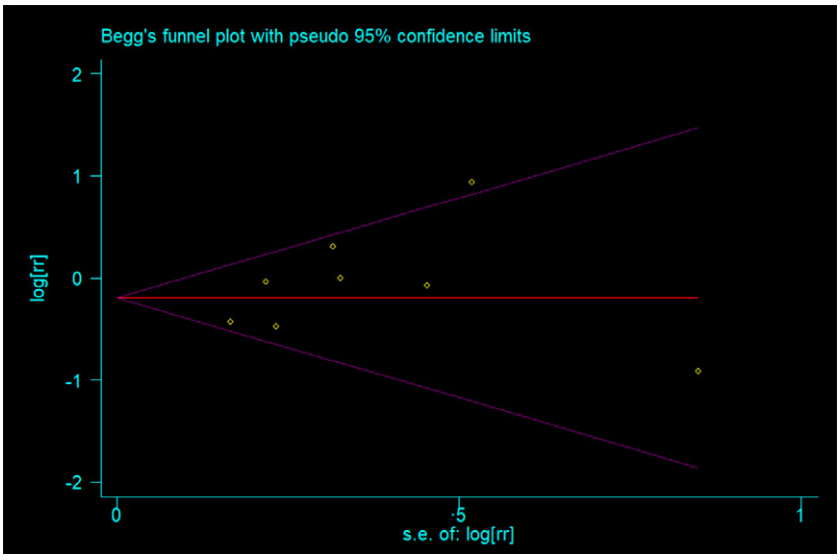

Fig. 4. Funnel plots analysis to detect publication bias in heavy alcohol drinking *v.* non-drinking.

signalling pathways, for example, disruption of the activation of transcription factors, suppression of multiple protein kinases and regulation of the expression of genes which related to cell proliferation, angiogenesis and apoptosis[29,30]. Second, laboratory evidence has also shown that certain components of red wine, such as phenols, may play an important role in reducing

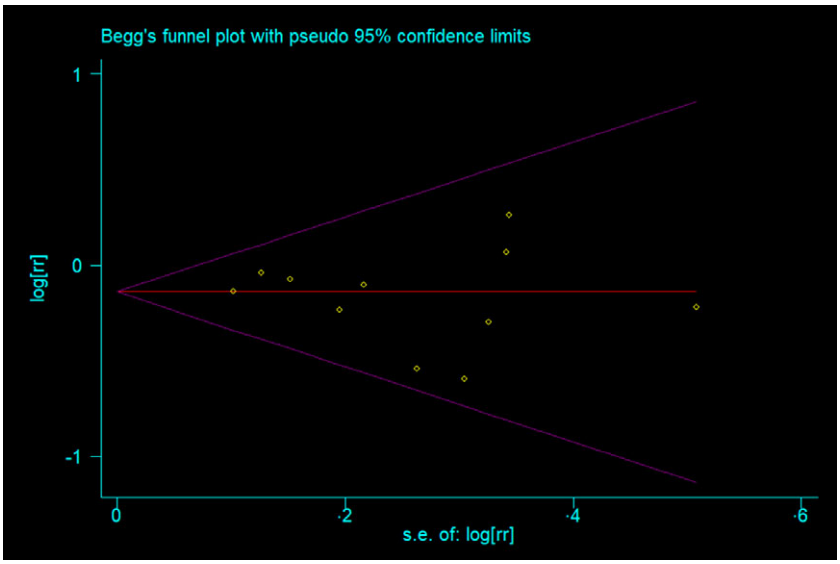

Fig. 5. Funnel plots analysis to detect publication bias in the light–moderate alcohol drinking *v.* non-drinking.

Table 2. Alcohol intake and glioma: sensitivity analysis (Risk ratio and 95 % confidence intervals)

Study characteristic	Category	Number	Heavy alcohol drinking	95 % CI	Low–moderate alcohol drinking	95 % CI
Age	>50	5	0·80	0·55, 1·17	0·88	0·78, 0·99
	<50	3	1·12	0·75, 1·67	0·78	0·56, 1·11
Sex	Men	3	0·90	0·44, 1·83	0·91	0·74, 1·12
	Women	3	0·80	0·59, 1·07	0·85	0·73, 0·98
	Men and women	5	1·16	0·50, 2·69	0·88	0·66, 1·19
Ethnicity	White	7	0·89	0·67, 1·18	0·87	0·78, 0·97
	Other	1	–		0·80	0·30, 2·17
Study design	Case–control	3	1·12	0·75, 1·67	0·78	0·56, 1·11
	Cohort	5	0·80	0·55, 1·17	0·88	0·78, 0·99

the growth and development of glioma[31]. These mechanisms mentioned above could explain the observed association between low–moderate alcohol drinking and risk of glioma. Meanwhile, in this study, we observed no significant association between heavy alcohol drinking and glioma risk. Our results are inconcordant with a previous study[12], which suggests that alcohol consumption increases the risk of glioblastoma consistent with a dose–response relationship. Alcohol drinking has been consistently considered as an important risk factor for cancers[32]. Data from the Melbourne Collaborative Cohort Study including sixty-seven glioblastoma cases showed no significant differences for those drinking<20 g/d of alcohol, but a higher risk for those drinking 40–59 g/d (HR = 3·07, 95 % CI (1·26, 7·47)) and ≥60 g/d (HR = 2·54, 95 % CI (0·92, 7·00)), compared with lifetime abstainers[12]. Although we observed no significant association between heavy alcohol drinking and glioma risk in this study, several plausible mechanisms have also been proposed. First, alcohol is an identified human carcinogen that penetrates the blood–brain barrier and thus may play an important role in the development of glioma[11]. Second, acetaldehyde is an intermediate product of alcohol metabolism, which have been shown to induce DNA lesions, generate free radicals and damage enzymes involved in DNA repair and antioxidant protection[33]. Third, animal studies have also shown that N-nitroso compounds contained in alcohol can result in brain tumours[8]. In a hospital-based case–control study, Hurley et al. found no significant association between heavy alcohol consumption and risk of glioma in both men and women[10]. However, the risk estimate was only adjusted for age and reference rate, and residual confounding was possible. In case–control studies of alcohol consumption in particular, the risk of recall bias may be substantial, and this bias may affect the relationship between alcohol intake and glioma risk[34]. There are several possible explanations for the null association. First, alcohol intake might have changed during the follow-up, such as after a diagnosis of glioma. This change in alcohol intake could attenuate the association between heavy alcohol drinking and the risk of glioma. Second, we were unable to analyse the effect of specific alcohol types on glioma, because limited data were available. Finally, to the above-mentioned, some constituents in alcoholic beverages, for example, beer, red wine have been reported to have anticancer properties[30,31].

Strengths and limitations

This systematic review and meta-analysis had its own strengths and limitations. First, this is the latest systematic review and meta-analysis on alcohol intake in relation to the risk of glioma. We not only have an update on the earlier meta-analysis (Qi *et al.* in 2014)[14] but also further clarify the relationship between heavy alcohol drinking and low–moderate alcohol drinking and glioma risk. Second, the cases of glioma have been diagnosed through clinical manifestations, pathological section or endoscopic ultrasonography, avoiding misdiagnosis. Third, no signs of publication bias were evident in the funnel plot, and the statistical test for publication bias was non-significant. However, several limitations should be noted in this study. First, due to this meta-analysis was based on observational studies (i.e. case–control or cohort design), confounding factors are often of concern. Thus, we cannot rule out the probability that these findings were susceptible to recall and selection bias. Second, there was an inconsistent adjustment for potential confounders in the included studies. As a result, the data included in our analysis might suffer from differing degrees of completeness and accuracy. Third, because of scanty data be available in included studies, we were unable to assess separately various types of glioma, for example, glioblastoma and oligodendroglioma. Finally, the potential publication bias may distort the relationship between alcohol intake and glioma risk.

Conclusion

In conclusion, this systematic review and updated meta-analysis suggests an inverse association between low–moderate alcohol drinking and the risk of glioma. However, the lack of a dose–risk relationship for these findings indicates caution in their interpretation. Our findings need to be affirmed in further randomised controlled trials or large prospective studies.

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The authors' responsibilities were as follows: L. S. and F.-B. J. took responsibility for data integrity and the accuracy of data analysis; L. S. was responsible for study concept and design; F.-B. J. and D. Y. acquired the data; L. S. and D. Y. were responsible for analysis and interpretation of the data; L. S. performed the statistical analysis; and F.-B. J. and L. S. drafted the manuscript. All authors critically revised the manuscript for important intellectual content.

The authors declare no conflict of interest associated with this paper.

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