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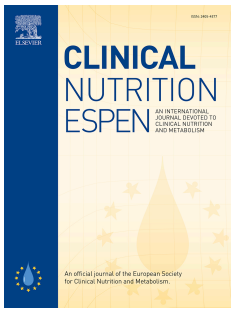

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Effects of Coffee and Tea Consumption on Glioma Risk: An Umbrella Review of Systematic Reviews and Meta-analyses

Hamid Abbasi[1,2], Emad Alem[3], Farnush Bakhshimoghaddam[4], Sara khoshdooz[5], Saeid Doaei[6*]

1. *Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran.*
2. *Neurosciences Research Center (NSRC), Tabriz University of Medical Sciences, Tabriz, Iran.*
3. *Department of Clinical Nutrition and Dietetics, Faculty of Nutrition Sciences and Food Technology, National Nutrition and Food Technology Research Institute, Shahid Beheshti University of Medical Sciences, Tehran, Iran*
4. *Department of Nutrition, School of Allied Medical Sciences, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.*
5. *Faculty of Medicine, Guilan University of Medical Science, Rasht, Iran.*
6. *Department of Community Nutrition, Faculty of Nutrition and Food Technology, National Nutrition and Food Technology Research Institute, Shahid Beheshti University of Medical Sciences, Tehran, Iran.*

Hamid Abbasi

Email address: Hamidabbasisaeed5@gmail.com, h.abbasi@tbzmed.ac.ir

ORCID: 0009-0007-5669-1591

Emad Alem

Email address: e.alemnut@gmail.com

ORCID: 0000-0001-6527-238x

Farnush Bakhshimoghaddam

Email address: farnushbakhshimoghadam@gmail.com

ORCiD: 0000-0002-5117-2633

Sara khoshdooz

Email address: Dr.khoshduz@gmail.com

ORCiD: 0000-0001-9872-7993

*** Corresponding Author: Saeid Doaei**

Department of Community Nutrition, Faculty of Nutrition and Food Technology, National Nutrition and Food Technology Research Institute, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Email: doaei@gums.ac.ir

ORCID: 0000-0002-2532-7478

Abstract

Background: Coffee and tea are considered to have some effects on glioma as one of the most prevalent intracranial malignant tumors in adults. However, the precise effect of coffee and tea consumption on glioma is not obvious. This umbrella review aimed to evaluate the impact of tea and coffee consumption on glioma risk.

Methods: Three online databases containing Scopus, Web of Science, and PubMed were thoroughly searched from the beginning to February 23, 2024 with no language constraints. Relying on I^2 and Q statistics, a random-effect model or a fixed-effect model was applied. The PICO structure was followed as Population (Patients with glioma), Intervention (Coffee and tea consumption), Comparison (Standard treatment or placebo), and Outcome (Risk of glioma).

Results: Totally, seven meta-analyses and systematic reviews contain 23591 patients were included in this umbrella review. Coffee and tea consumption led to significant 15% and 16% reductions in glioma risk, respectively (RR= 0.85; 95% CI: 0.74, 0.98; RR= 0.84; 95% CI: 0.79, 0.89). The results did not change after subgroup analyses.

Conclusion: This umbrella review revealed that the coffee and tea consumption may decrease the glioma risk. Consumption of tea and coffee may be considered as dietary strategies against glioma.

PROSPERO registration code: CRD42024521525

Keywords: Glioma; coffee; tea; umbrella review

Introduction

Glioma is a malignant brain tumor in adults that originates from the glial cells of the brain and accounts for about 70.9%% of all cancers of the central nervous system (1). The annual incidence of glioma in American adults is reported to be 5 per 1,000,000 people (2). Glioma represents a serious disease burden because it is prone to recurrence, rapid onset, low morbidity, and high mortality (3). There are several risk factors associated with glioma including genetic predisposition, allergic disorders, higher age, male sex, European ethnicity, environmental exposures such as ionizing radiation, and dietary unhealthy habits (4).

The role of diet in the etiology of glioma is less well understood. However, various dietary factors are reported to promote or prevent brain cancer (5). Among the dietary factors, the effect of tea and coffee as popular drinks on glioma has recently received considerable attention (6). Coffee and tea contain potentially anticancerogenic compounds such as vitamin precursors, minerals, antioxidants, and phenols (7). The polyphenols found in coffee and tea such as phenolic acids and flavonoids, have been shown to protect against glioma by regulating xenobiotic metabolizing enzymes, modulating heterogeneous metabolic enzymes, and suppressing tumor growth (8). The protective effect of coffee and tea against glioma may also be attributed to the fact that epigallocatechin-3-gallate, kahweol, and cafestol inhibit DNA methyltransferase and reactivate genes silenced by DNA methylation (9, 10).

While many studies have been done on the association between coffee and tea consumption with the risk of glioma, the results of studies are still controversial. Several meta-analyses and systematic studies have explored the impact of caffeinated drinks, such as coffee and tea on the risk of glioma (5, 11, 12, 13, 14, 15). One study after pooling included papers with 2100 cases found that tea unlike coffee was significantly linked to reducing the glioma risk (11). A dose-response meta-study found that consuming one cup of coffee and tea per day was associated

with a 3% reduction in the risk of glioma (13). A meta-paper of prospective cohort papers revealed that one cup of tea per day was unrelated to glioma risk reduction (12). An updated meta-study reported a 24% decrease in glioma risk after coffee consumption by pooling 10 included papers (14). However, there is still no consensus on the effect of tea and coffee on the risk of glioma (16). In the present Umbrella study, to provide a quantitative overall estimate on the effect of tea and coffee on glioma risk, we collected existing systematic reviews and meta-analyses to shed light on the link between coffee and tea and the risk of glioma using the umbrella review method.

Methods

In congruence with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines, the present umbrella review of systematic reviews and meta-analyses was executed (17). The umbrella review protocol was ultimately registered in PROSPERO (ID: CRD42024521525).

Search strategy

Three online databases containing Scopus, Web of Science, and PubMed were thoroughly searched up to February 23, 2024 with no language constraints using Medical Subject Heading (MeSH) words, OR, and AND operators. The following advanced search was utilized in PubMed: ((((("Caffeine"[Mesh]) OR "Coffee"[Mesh]) OR "Tea"[Mesh]) OR (((("caffeine"[Title/Abstract]) OR ("coffee"[Title/Abstract])) OR ("tea"[Title/Abstract]))) AND ((((("Glioma"[Mesh]) OR "Glioblastoma"[Mesh]) OR "Brain Neoplasms"[Mesh]) OR ((((("glioma"[Title/Abstract]) OR ("glioblastoma"[Title/Abstract])) OR ("brain cancer"[Title/Abstract])) OR ("brain neoplasms"[Title/Abstract])))). Double quotation mark was used to enhance the sensitivity of our advanced search. To prevent from missing any new

publications, one of the investigators (H.A) activated the e-mail alert service of PubMed. The search strategy of scientific databases is described in Supplementary Material 1.

Eligibility criteria

On the basis of the following criteria, papers were considered to include in this umbrella review: (1) full-text publications of systematic review and/or meta-analysis with no language and publication year constraints; and (2) evaluated the impact of coffee and tea consumption on glioma risk. Quasi-experimental publications, observational studies, case-reports, reviews, commentaries, case-series, letters, and animal studies were excluded from this umbrella review. To conduct this umbrella review, the following PICO structure was used: Population (Patients with glioma); Intervention (Coffee and tea consumption), Comparison (Standard treatment or placebo), and Outcome (Risk of glioma).

Study selection

Via EndNote software, duplicate publications were omitted by an author (H.A.). According to the eligibility criteria and PICO, titles/abstracts and full-text of remaining research were separately screened by two authors (F.B and S.KH) and then inspected by the first and corresponding author (H.A and S.D).

Methodological quality assessment

One of the authors (H.A) assessed the included systematic reviews and meta-analyses and eventually checked by the corresponding author (S.D). In accordance with the type of studies, the assessment of multiple systematic reviews (AMSTAR)-2 was considered to assess the risk of bias of included papers. The aforementioned tool was developed for assessing the systematic review and meta-analysis quality which included 7 critical domains with 16 questions. In the AMSTAR-2 tool, the questions were answered based on a “No meta-analysis” or “Partial Yes”

or “NO” or “Yes” which the overall quality of papers was reported according to the “High”, “Moderate”, “Low”, and “Critically low” (18).

Data extraction

The first author (H.A) extracted the acquired data into a pre-designed Microsoft Word table which was meticulously checked by the corresponding author (S.D). The data in the table contains the following details: (1) the first author’s name; (2) publication year; (3) location and duration; (4) total cases; (5) risk factors along with the precise number of included studies (coffee and/or tea); (6) summary of relative risk (RR) with the corresponding 95% confidence interval (CI); (7) I^2 statistic with its p-value; (8) quality assessment scale. The aforesaid details are depicted in Table 1.

Data synthesis and statistical analysis

The RR in conjunction with their 95% CI was used for estimating the overall effect size. Relying on I^2 and Q statistics, a correct statistics approach was chosen either a random-effect model or a fixed-effect model (19, 20). When $I^2 > 75\%$, it was thoroughly considered to exhibit high heterogeneity, whereas $I^2 \leq 40\%$ demonstrated low heterogeneity (21). To anticipate potential heterogeneity sources, subgroup analysis was performed in which total cases, included studies, risk of bias, AMSTAR, and country were considered. In Table 3, the results of the subgroup analysis are depicted. The publication bias of the studies based on the graphical method of funnel plot was evaluated with two various visual inspections (asymmetry and symmetry, respectively). To rectify the papers’ publication bias, the Trim and Fill method was applied. Our statistical analyses were entirely conducted using R Studio software version 2023.03.1 along with R software version 4.3.2. The R package of metagen was utilized to estimate pooled RR. The meaningful level was set at $P \leq 0.05$.

Results

Study selection

In this umbrella review, meta-analyses and systematic reviews were utilized. The years of papers included in the present umbrella review ranged from 2013 to 2022. As illustrated in Figure 1, based on advanced literature searches, 629 eligible papers were obtained. After omitting duplicated records, 462 papers were meticulously screened via titles/abstracts, of which 453 papers were ultimately excluded. Subsequently, in accordance with the research topic, 9 papers were achieved for full-text assessment, of which 2 papers were eventually excluded from this umbrella review encompassing one letter (22) and one cohort study (23).

Demographic characteristics of the included studies

The basic characteristics of the included papers are demonstrated in Table 1. The overall cases of these 7 included papers were 23591 patients. The cases differed from 1582 to 8831 in the mata-analyses. The mediocre number of included papers of meta-analyses and systematic reviews varied between 6 and 113. Out of 7 selected papers, 4 papers were executed in China (5, 12, 14, 15), one paper in Indonesia (13), one paper in Iran (24), and the remaining paper in Italy (11). Seven included papers evaluated the role of coffee (n= 5) and tea (n= 7) consumption on the risk of glioma, of which 6 papers were included in the quantitative analysis section of the umbrella review (5, 11, 12, 13, 14, 15).

Methodological quality assessment

According to the AMSTAR-2, the methodological quality assessment is presented in Table 2. From 7 systematic reviews and meta-analyses, five of the selected papers were of moderate quality (5, 12, 13, 14, 15), one was low quality (11), and one paper was critically low quality (24).

Association between coffee consumption and glioma risk

After pooling four selected papers that reported the effect of coffee consumption on the risk of glioma, a significant 15% reduction in glioma risk was detected (RR= 0.85; 95% CI: 0.74, 0.98) (Figure 2A). Howbeit, an insignificant low heterogeneity was observed among papers (I^2 = 0%, *P*=0.39). Analysis of publication bias revealed that the graphical shape of the funnel plot was asymmetric (Figure 2B). Besides that, the trim and fill method was applied for small-study effect evaluation, which resulted in a change in the pooled RR after removing the two selected meta-studies (RR= 0.91; 95% CI: 0.81, 1.02) (13, 14).

Association between tea consumption and glioma risk

The selected papers that assessed the impact of tea consumption on glioma risk were entered into the umbrella review analysis. The pooled RR indicated that tea consumption meaningfully decreased the glioma risk by 16% (RR= 0.84; 95% CI: 0.79, 0.89) (Figure 3A) with a low insignificant between-study heterogeneity (I^2 = 0%, *P*=0.99). The asymmetric graphical inspection substantiated the publication bias presence (Figure 3B). Moreover, the small-study effect was detected among the six included papers. Ultimately, three meta-papers were omitted (RR= 0.85; 95% CI: 0.81, 0.89) (5, 12, 15).

Discussion

The results of this umbrella review confirm a negative association between coffee and tea consumption and the risk of glioma. Tea and coffee consumption may significantly decrease glioma risk by 15% and 16%, respectively. In previous studies, inconsistent associations have been observed between caffeine intake, tea, coffee, and other caffeinated drinks, and glioma risk (5, 13, 25). The literature is challenging to interpret because most studies report only one or a combination of these beverages as risk factors for glioma. In line with the present study,

Creed et al. observed that consuming four cups or more of tea daily was associated with a lower incidence of glioma and had the same impact on glioblastoma (HR = 0.93 per cup/day increase; 95%CI: 0.89–0.98) (16). Analysis of tea subgroups revealed low, insignificant heterogeneity among subgroups. A larger sample size in future studies could further elucidate the impact of tea and coffee intake on brain cancer risk. Notably, the beneficial effects appeared more pronounced in the Chinese population. Although Cote et al., did not find a significant association between caffeine, decaffeinated coffee intake, and total coffee intake and glioma risk (25). Other studies have shown a negative association between tea and coffee consumption and the probability of developing glioma (16, 26). Only the Zhao et al. study explored the separate impact of both green and black tea on various cancer risks, indicating an insignificant rise in glioma risk after green tea consumption (13). Different types of studies confirm our findings (26, 27), suggesting that consuming tea lowers the probability of developing glioma, and the findings remained significant even when sensitivity analysis and subgroup analysis were performed.

The exact mechanisms of the effects of coffee and tea on glioma are not yet clear. Polyphenols in tea including epigallocatechin gallate (EGC) gallate and EGC gallate, have been linked to preventing various cancers (28). Through the activation of apoptosis in vitro, it has been shown that EGC gallate and EGC can inhibit the proliferation of breast cancer cells (29). It has been shown in several investigations that EGC and its derivatives can cross the blood-brain barrier and reach the brain parenchyma in response to the administration of EGC gallate and EGC supplementation (28, 30, 31, 32). Several studies have shown that epigallocatechin gallate can trigger apoptosis, inhibit cell proliferation, and restrict the invasion of different glioma cell lines. Coffee and tea both include methylxanthines, such as theophylline and caffeine, which possess anti-inflammatory properties and promote the generation of cerebrospinal fluid (33). These diminutive lipophilic compounds can traverse the blood-brain barrier to aid in the

236 removal or dilution of neurotoxins, therefore diminishing the possibility of glioma (16).
237 Nevertheless, the impact on the advancement of cancer might differ due to the extensive range
238 of brewing techniques and distinct varieties of coffee and tea (14).

239 Coffee is abundant in polyphenols, such as flavonoids and phenolic acids (34), which are
240 recognized for their anticancer properties, ability to regulate heterogeneous metabolite
241 enzymes, and ability to inhibit tumor progression (35). These compounds are also associated
242 with cancer prevention (36, 37). Furthermore, coffee contains diterpenes and caffeic acid,
243 which may provide cancer protection (38). Also, coffee is known to contain chlorogenic acid,
244 which is responsible for several biological properties, including anticarcinogenic, antioxidant,
245 and antibacterial activity. Furthermore, it has been suggested that coffee can enhance insulin
246 sensitivity or glucose tolerance in vivo by stimulating AMP-activated protein kinase (39).
247 Similar effects have been reported for caffeic acid, a metabolic product of chlorogenic acid
248 (40). According to recent studies, AMPK activation may have anticarcinogenic effects (41).
249 Furthermore, Cafestol and kahweol, two coffee diterpenes, are also known to affect O6-
250 methylguanine-DNA methyltransferase (MGMT), a DNA repair protein, in vitro and may have
251 antiangiogenic properties (42). Activating the Nrf2/ARE pathway is another crucial
252 mechanism for protecting cells and tissues against carcinogenesis and carcinogenic metabolites
253 (43). Several coffee constituents, including those produced during the roasting process,
254 contribute to the Nrf2-translocating properties of coffee, according to a recent study.
255 Nonetheless, for the chemo preventive properties of the final coffee product, it appears that the
256 formation and degradation of activating and deactivating constituents must be precisely
257 regulated during its roasting (44).

258 The contribution of coffee and tea protection against oxidative stress is being extensively
259 investigated (25, 35). Elevated ROS levels have been shown to promote mutagenic DNA

damage, and Nrf2 plays a role in mediating the expression of critical protective enzymes through the antioxidant-response element (ARE) (45). Additionally, ROS has been found to play an essential role in hematopoietic stem cell (HSC) regulation, and Nrf2 has been recognized as a master transcriptional factor that regulates multiple antioxidant enzymes (46). Furthermore, while ROS are elevated during cancer and have been shown to activate signaling pathways involved in cell proliferation and migration, as well as cause DNA damage leading to mutations, the NRF2 program is usually regarded to be beneficial, indicating the complex role of ROS and Nrf2 in cellular processes (47).

Strengths and limitations

The present study had several strengths. This umbrella review included prospective studies with comparable data. Case-control studies may be susceptible to bias as a result of the psychological stress encountered by recently diagnosed patients and the symptoms associated with the condition, which may affect their capacity for recall or their motivation to fill out questionnaires. Prospective cohorts are less prone to bias caused by data collection under a less demanding physical health condition and provide a more comparable baseline. However, studies that use both questionnaires and interviews to gather coffee/tea data are anticipated to provide a higher standard of data compared to studies that rely only on questionnaires. Moreover, we have low heterogeneity, especially in tea groups and our inclusion criteria and analysis were matched together.

However, our study had some limitations. First, bias might arise from the various measuring techniques used in the included research. Secondly, there are variations in the duration of follow-up across the studies, which could have added to the heterogeneity. The impact estimate may change depending on the follow-up period since it is uncertain whether the increase in coffee and tea has the same effect or diminishes with time. Third, two studies had low quality

based on AMSTAR-2. Fourth, the asymmetric graphical inspection substantiated the presence of publication bias. Ultimately, we were unable to manage all the variables that may influence the outcome, resulting in a certain level of deviation. More studies are required to determine a borderline range of tea and coffee intake for the dose-response relationship.

Conclusion

The results of this umbrella review of meta-analysis and systematic reviews indicated that coffee and tea consumption can significantly reduce the glioma risk. If confirmed in future studies, the consumption of tea and coffee may be considered as dietary strategies against the risk of glioma. Further research with assorted dosages of coffee and tea intake as well as longer durations are warranted to confirm these results and to discover the underlying mechanisms of the effect of coffee and tea on glioma.

Ethics approval and consent to participate

Note applicable.

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None.

Authors' Contribution

H.A: systematic search; F.B, S.KH: study selection; H.A: data extraction; H.A: risk of bias assessment, preparing the figures; H.A, E.A: drafting the manuscript; S.D: conceptualization; supervision and critically editing the manuscript. All authors approved the final version for submission.

Consent for publication

Note applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary files.

Declaration of competing interest

The authors assert that they have no conflicts of interest.

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Note applicable.

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Tables

Table 1. Study characteristics of systematic reviews and meta-analyses in the umbrella review.

Study, date	Number of included studies	Location, Duration	Total cases (n)	Risk factor (number of studies)	Effect size metric	Summary of effect size (95%CI)	I^2(%)	*P*-heterogeneity	Quality assessment scale
Malerba et al. 2013 (11)	6	Italy 1987-2012	2075	Coffee (5) Tea (3)	RR	0.96 (0.81, 1.13) 0.86 (0.78, 0.94)	22.6 0	0.271 0.419	NR
Zhang et al. 2015 (15)	87	China 1986-2012	1582	Tea (3)	RR	0.83 (0.68, 1.02)	9.9	0.343	NOS
Malmir et al. 2015 (24)	14	Iran 1987-2016	3150	Coffee (12) Tea (8)	NR	NR	NR	NR	NOS
Song et al. 2019 (14)	11	China 1987-2017	2583	Coffee (10) Tea (7)	RR	0.760 (0.548, 0.972) 0.846 (0.683, 1.047)	63.9 24.6	0.003 0.241	NR
Pranata et al. 2021 (13)	13	Indonesia 1986-2020	2987	Coffee (12) Tea (9)	RR	0.77 (0.55, 1.06) 0.84 (0.71, 0.98)	75.27 16.42	0.001 0.19	NOS
Zhao et al. 2021 (12)	113	China 2010-2020	2383	Tea (6)	RR	0.81 (0.70, 0.95)	2.7	NR	NOS
Zhang et al. 2022 (5)	33	China 1986-2021	8831	Coffee (12) Tea (10)	RR	0.81 (0.62, 1.06) 0.82 (0.71, 0.93)	61.2 23.2	0.003 0.230	NOS

Abbreviations: CI: confidence interval; NR: not reported; RR: relative risk; NOS: Newcastle–Ottawa Scale

Table 2. Results of the selected systematic reviews and meta-analyses based on AMSTAR 2.

Study, date	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Overall
Malerba et al. 2013 (11)	Y	Y	Y	Y	Y	N	N	Y	N	N	Y	N	N	Y	N	N	Low
Zhang et al. 2015 (15)	Y	Y	Y	Y	Y	Y	Y	N	N	N	PY	Y	Y	PY	Y	Y	Moderate
Malmir et al. 2017 (24)	Y	Y	Y	N	N	Y	Y	N	N	N	NM	NM	Y	N	NM	Y	Critically low
Song et al. 2019 (14)	Y	N	Y	N	N	Y	PY	N	Y	Y	Y	N	Y	N	N	Y	Moderate
Pranata et al. 2021 (13)	Y	N	Y	Y	Y	Y	N	Y	Y	N	Y	N	Y	Y	N	N	Moderate
Zhao et al. 2021 (12)	Y	Y	Y	N	N	Y	Y	Y	Y	N	N	N	Y	Y	N	N	Moderate
Zhang et al. 2022 (5)	Y	N	Y	Y	Y	Y	N	Y	Y	N	Y	N	Y	Y	N	N	Moderate

Abbreviations: Y, Yes; PY, Partially Yes; N, No; NM: No Meta-analysis; Questions: Q1- Did the research questions and inclusion criteria for the review include the components of PICO? Q2- Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review, and did the report justify any significant deviations from the protocol? Q3- Did the review authors explain their selection of the study designs for inclusion in the review? Q4- Did the review authors use a comprehensive literature search strategy? Q5- Did the review authors perform study selection in duplicate? Q6- Did the review authors perform data extraction in duplicate? Q7- Did the review authors provide a list of excluded studies and justify the exclusions? Q8- Did the review authors describe the included studies in adequate detail? Q9- Did the review authors use a satisfactory technique for assessing risk of bias (RoB) in individual studies that were included in the review? Q10- Did the review authors report on the sources of funding for the studies included in the review? Q11- If meta-analysis was performed, did the review authors use appropriate methods for the statistical combination of results? Q12- If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? Q13- Did the review authors account for RoB in individual studies when interpreting/discussing the review results? Q14- Did the review authors provide a satisfactory explanation for and discussion of any heterogeneity observed in the review results? Q15- If they performed quantitative synthesis, did the review authors conduct an adequate investigation of publication bias (small-study bias) and discuss its likely impact on the review results? Q16- Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

Table 3. Subgroup analysis for the impact of tea and coffee consumption on glioma risk.

Drink type	Effect size (number)	RR (95% CI)	I^2(%)	P-heterogeneity
Coffee				
Overall	4	0.85 (0.74, 0.98)	0	0.39
Participants				
>2600	2	0.79 (0.64, 0.98)	0	0.81
≤2600	2	0.88 (0.71, 1.10)	48	0.17
Included studies				
>12	2	0.79 (0.64, 0.98)	0	0.81
≤12	2	0.88 (0.71, 1.10)	48	0.17
Risk of bias				
NOS	2	0.79 (0.64, 0.98)	0	0.81
NR	2	0.88 (0.71, 1.10)	48	0.17
AMSTAR				
Moderate	3	0.78 (0.66, 0.93)	0	0.95
Low	1	0.96 (0.81, 1.13)	-	-
Country				
Chinese	2	0.79 (0.65, 0.96)	0	0.75
Non-Chinese	2	0.90 (0.74, 1.10)	28	0.24
Tea				
Overall	6	0.84 (0.79, 0.89)	0	0.99
Participants				
>2500	3	0.83 (0.76, 0.91)	0	0.96
≤2500	3	0.84 (0.78, 0.91)	0	0.79
Included studies				
>30	3	0.82 (0.75, 0.90)	0	0.98

≤30	3	0.85 (0.79, 0.92)	0	0.97
Risk of bias				
NOS	4	0.82 (0.76, 0.89)	0	0.99
NR	2	0.86 (0.79, 0.93)	0	0.89
AMSTAR				
Moderate	5	0.83 (0.77, 0.89)	0	1
Low	1	0.86 (0.78, 0.94)	-	-
Country				
Chinese	4	0.82 (0.76, 0.89)	0	0.99
Non-Chinese	2	0.85 (0.79, 0.93)	0	0.80

RR: risk ratio; NR: not reported

Figures

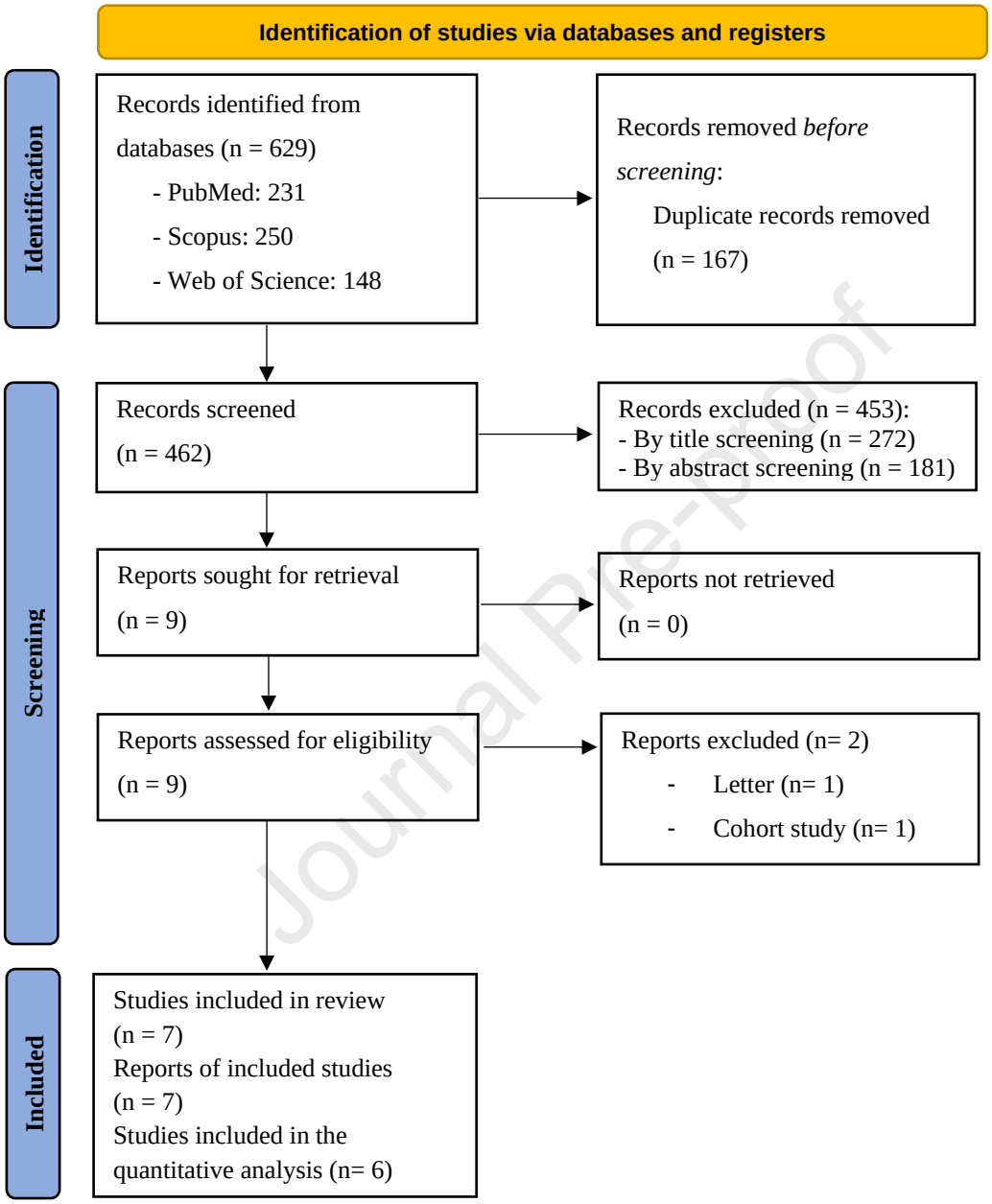
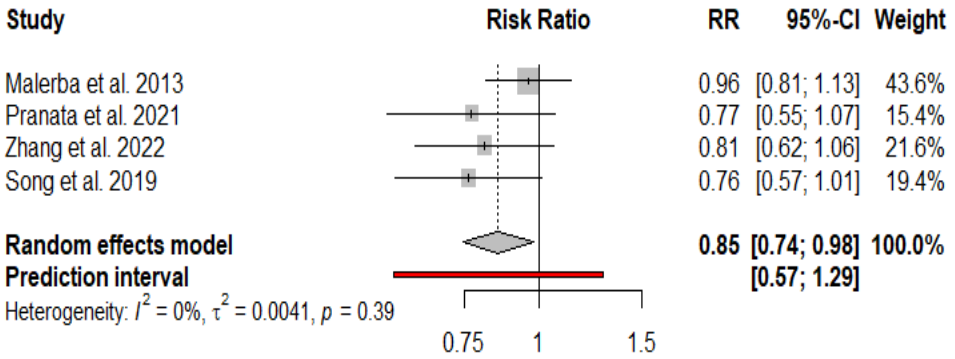
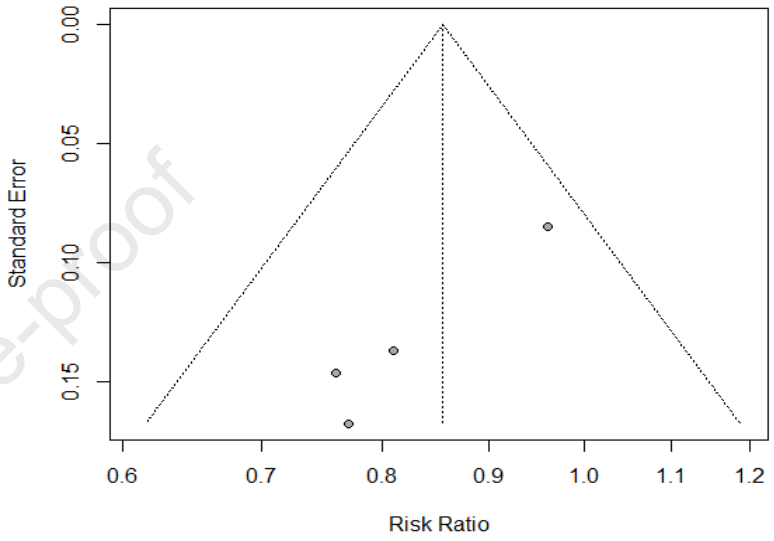


Figure 1. PRISMA flow chart of umbrella review

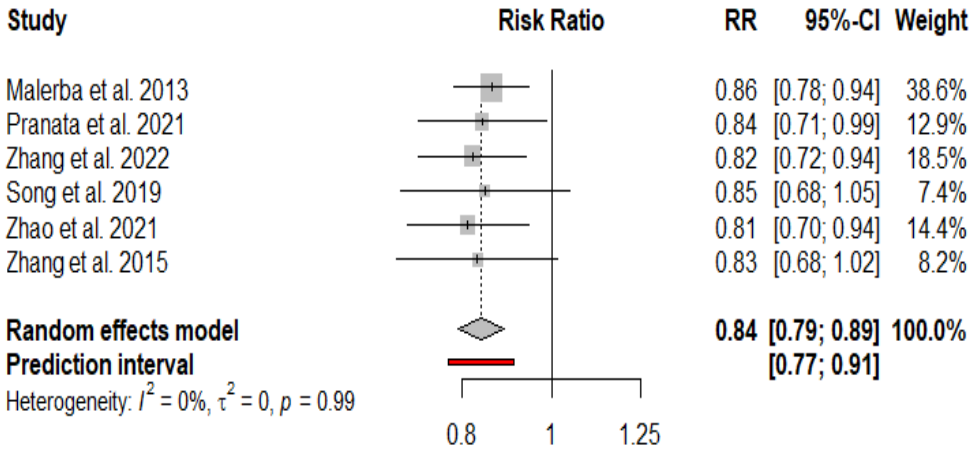


2A



2B

Figure 2. Umbrella review of meta-analyses examining the effect of coffee consumption on glioma risk. Forest plot (A) utilizing RR with 95% CI; Funnel plot (B) of selected meta-analyses



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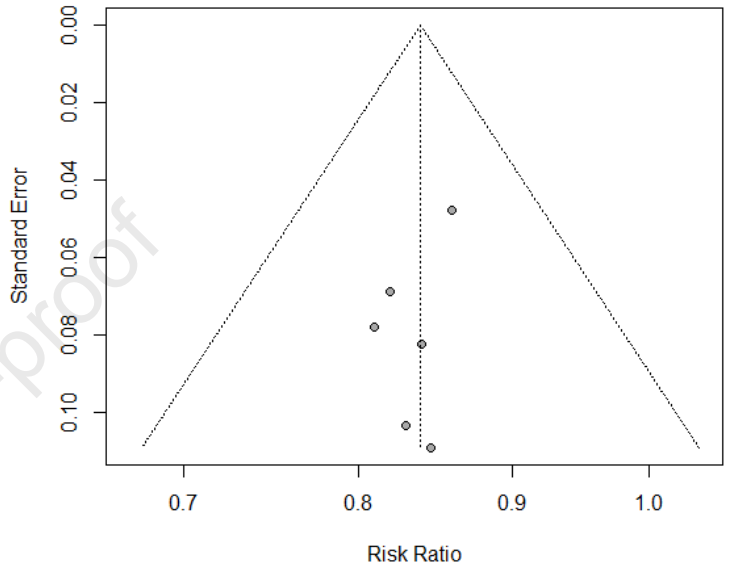

3B

Figure 3. Umbrella review of meta-analyses examining the effect of tea consumption on glioma risk. Forest plot (A) utilizing RR with 95% CI; Funnel plot (B) of selected meta-analyses