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Coffee and tea consumption and the risk of glioma: a systematic review and dose–response meta-analysis

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Abstract

In this systematic review and dose–response meta-analysis, we aimed to assess whether coffee and tea consumption is related to the risk of glioma. We performed a systematic literature search using PubMed, Embase, Scopus and the EuropePMC from the inception of database up until 1 October 2020. Exposures in the present study were coffee and tea consumption, the main outcome was the incidence of glioma. The present study compares the association between the exposure of coffee and tea with the incidence of glioma, and the results are reported in relative risks (RR). There are 12 unique studies comprising of 1 960 731 participants with 2987 glioma cases. Higher coffee consumption was associated with a statistically non-significant trend towards lower risk of glioma (RR 0·77 (95 % CI 0·55, 1·03), $P = 0·11$; I^2:75·27 %). Meta-regression showed that the association between coffee and glioma was reduced by smoking ($P = 0·029$). Higher tea consumption was associated with a lower risk of glioma (RR 0·84 (95 % CI 0·71, 0·98), $P = 0·030$; I^2:16·42 %). Sensitivity analysis by removal of case–control studies showed that higher coffee consumption (RR 0·85 (95 % CI 0·72, 1·00), $P = 0·046$; I^2:0 %) and higher tea consumption (RR 0·81 (95 % CI 0·70, 0·93), $P = 0·004$; I^2:0 %, $P_{\text{non-linearity}} = 0·140$) were associated with lower risk of glioma. Dose–response meta-analysis showed that every one cup of coffee per day decreases the risk of glioma by 3 % (RR 0·97 (95 % CI 0·94, 0·99), $P = 0·016$, $P_{\text{non-linearity}} = 0·054$) and every one cup of tea per day decreases the risk of glioma by 3 % (RR 0·97 (95 % CI 0·94, 1·00), $P = 0·048$). This meta-analysis showed apparent association between coffee and tea intake and risk of glioma.

Key words: **Brain tumour: Caffeine: Cancer: Oncology: Glioma**

Glioma is a central nervous system tumor that originates from the glial cells of human brain and represents about 80 % of adult malignant brain cancers[1]. Some of the identified risk factors include male sex, advanced age, certain ancestry (European), allergic/atopic conditions and genetic predisposition, as well as ionising radiation from medical and environmental exposure[2,3]. However, the role of modifiable lifestyle-related factors and diet/nutrition, including coffee and tea consumption, is less well investigated[4].

The role of various nutritional factors in promoting or preventing brain cancer is increasingly being studied. Coffee and tea have long been popular drinks for people around the world and their consumption has been hypothesised to lower the risks of some cancers, including glioma[5]. Both beverages contain abundant amounts of polyphenols, including flavonoids (predominantly in tea) and phenolic acids (predominantly in coffee) which have been shown to protect against cancer due to their antioxidative properties, ability to regulate heterogenous metabolite enzymes and modulate xenobiotic metabolite enzymes, and inhibit tumour promotion[4,6]. Cumulative antioxidant capacity found in coffee is higher than that found in any given fruit and vegetable[7]. However, the benefit of coffee or tea consumption on the risk of glioma is still controversial; two most recent studies published in 2020 showed conflicting

Abbreviations: FFQ, Food Frequency Questionnaire; NOS, Newcastle Ottawa Scale; RR, Relative Risk.

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results, similar to previous studies[4,8]. In this systematic review and dose–response meta-analysis, we aimed to assess whether coffee and tea consumption is related to the risk of glioma by synthesising the latest evidence from cohort studies. We also aimed to quantify the relationship and whether it is linear through dose–response meta-analysis. Additionally, we aimed to explore the cause of heterogeneity among these studies by investigating potential confounders.

Material and methods

This systematic review and meta-analysis follows the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines. The protocol for this systematic review is registered in PROSPERO Database (CRD42020212303).

Eligibility criteria

We included research papers (both cohorts and case–control studies) that assessed the association between coffee and/or tea consumption with the risk of developing glioma. We excluded animal studies, abstract-only publications, preprints, review articles, commentaries, letters, case reports/series and studies that did not report key exposures and/or outcomes of interest.

Search strategy and study selection

We performed a systematic literature search using several electronic databases including PubMed, Embase, Scopus and the EuropePMC with keywords 'tea' OR 'coffee' OR 'caffeine' AND 'glioma' OR 'glioblastoma' OR 'brain cancer' for records published from inception up until 1 October 2020. The PubMed (MEDLINE) search strategy was ((tea)[All Fields] OR (coffee)[All Fields] OR (caffeine)[All Fields]) AND ((glioma)[All Fields] OR (glioblastoma) [All Fields] OR (brain cancer) [All Fields]). Full search strategy is supplied in Supplementary Figure 1. We also performed hand-searching for related articles. After compiling the initial records, duplicates were removed, and two authors independently assessed the titles and abstracts of the residual articles by applying inclusion and exclusion criteria. Authors in charge of performing literature searches are medical doctors with experience in performing systematic review and meta-analyses.

Data extraction

Two authors performed data extraction independently with the help of a standardised forms containing rows and columns for the first authors of the included studies, year, study design, age, sex, smoking status, alcohol drinking status, the outcome of interests and adjustment for covariates. These variables were chosen based on potential effect on the association between the exposure and key outcomes.

Exposures in the present study were coffee consumption and tea consumption. The main outcome of the present study was the incidence of glioma. The present study compared the association between the exposure of coffee and tea with the incidence of glioma, and the results were reported in relative risks (RR). We used the Newcastle–Ottawa Scale (NOS) to assess the risk of bias and the quality of the included studies. This was performed by two independent authors, and discrepancies that arise were resolved through discussion.

Statistical analysis

Meta-analysis was performed using STATA 16.0 (StataCorp LLC). Pooled effect estimates were reported in RR and its 95 % CI. We used random-effects model for all analyses regardless of heterogeneity. All *P*-values for the effect estimate were two-tailed, and a value of $\leq 0{\cdot}05$ was considered as statistically significant. Cochran's Q test and I^2 statistic were used to evaluate inter-study heterogeneity, and I^2 values > 50 % and *P*-value < 0·10 indicated significant heterogeneity. Studies with at least three quantitative classifications were eligible for dose–response meta-analysis. We performed a two-stage random-effects dose–response meta-analysis using generalised least-squares regression trend estimation based on log RR across coffee/tea consumption intervals. The potential for non-linear relationship was evaluated using restricted cubic splines with three-knot model. We used a restricted maximum likelihood multivariate random-effects meta-analysis to pool the effect estimates. A Wald-type test was used for evaluating non-linearity through testing regression coefficient of the second spline. Cote *et al.* study and Holick *et al.* were derived from the same cohort. Since Cote *et al.* was newer, it was included in the comparison between highest *v.* lowest category. However, only Holick *et al.* meets the requirement for dose–response analysis. Thus, both studies were included for different analysis. Regression-based Egger's test was performed to evaluate the presence of small-study effects and inverted funnel plot analysis for qualitative assessment of publication bias. In case of funnel plot asymmetry, non-parametric trim-and-fill analysis of publication bias with linear, L0 estimator was performed. Restricted maximum likelihood random-effects meta-regression analysis was performed for the association between coffee and the risk of glioma, using age, sex, continent of origin, smoking and drinking (alcohol) as covariates, one at the time. Sensitivity analysis was performed by removing case–control studies. Subgroup analyses that compared coffee consumption (4 cups/d *v.* < 1/d) and tea consumption (3–4 cups/d *v.* < 1/d) were performed, and these subgroup analyses were *post hoc* and determined based on the most frequent reporting.

Results

The flow chart for the study selection can be seen in Fig. 1. There were thirteen studies (twelve uniques studies) comprising of 1 960 731 participants with 2987 glioma cases included in this systematic review and meta-analysis[4,6,8–18]. The baseline characteristics of the included studies can be seen in Table 1. Cote *et al.* and Holick *et al.* studies were derived from the same cohorts. Only cohort studies were included in the dose–response analysis.

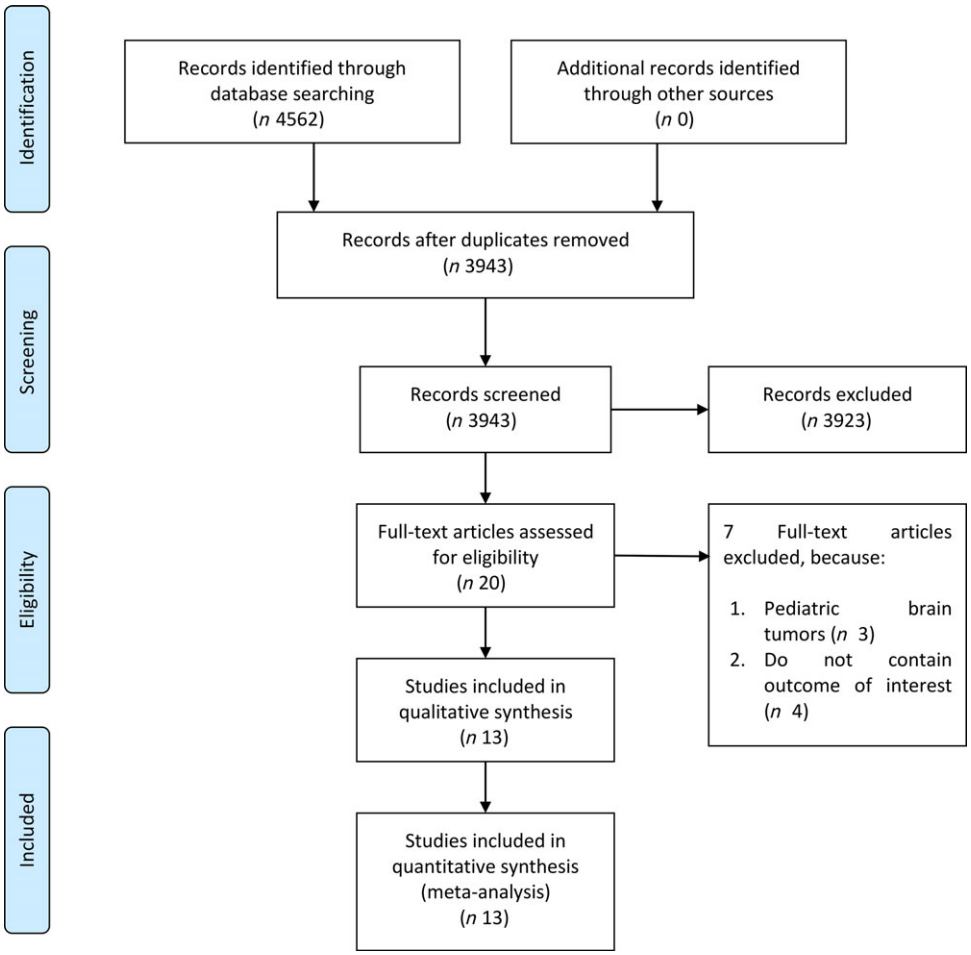

Fig. 1. Study flow diagram.

Highest v. lowest coffee consumption group

Higher coffee consumption was associated with a statistically non-significant trend towards lower risk of glioma (RR 0·77 (95 % CI 0·55, 1·03), $P = 0·11$; I^2:75·27 %, $P = 0·001$). Subgroup analysis for comparison between more than four cups per d *v.* less than one per d (five studies) showed a borderline significant result (RR 0·81 (95 % CI 0·64, 1·02), $P = 0·067$; I^2:0 %, $P = 0·602$). Dose–response meta-analysis showed that every one cup of coffee per d decreases the risk of glioma by 3 % (RR 0·97 (95 % CI 0·94, 0·99), $P = 0·016$). The dose–response relationship was borderline significant for non-linearity ($P_{\text{non-linearity}} = 0·054$) (Fig. 2(b)).

Highest v. lowest tea consumption group

Higher tea consumption was associated with the lower risk of glioma (RR 0·84 (95 % CI 0·71, 0·98), $P = 0·030$; I^2:16·42 %, $P = 0·19$). Subgroup analysis for comparison between more than three to four cups per d *v.* less than one per d (four studies) showed that tea was associated with risk reduction (RR 0·79 (95 % CI 0·65, 0·96), $P = 0·020$; I^2:10·01 %, $P = 0·373$). Dose–response meta-analysis showed that every one cup of tea per d decreases the risk of glioma by 3 % (RR 0·97 (95 % CI 0·94, 1·00), $P = 0·048$). The dose–response relationship was linear ($P_{\text{non-linearity}} = 0·140$) (Fig. 3(b)).

Sensitivity analysis

Sensitivity analysis by removal of case–control studies was performed. Higher coffee consumption was associated with reduced risk of glioma (RR 0·85 (95 % CI 0·72, 1·00), $P = 0·046$; I^2:0 %, $P = 0·230$). Higher tea consumption was associated with lower risk of glioma (RR 0·81 (95 % CI 0·70, 0·93), $P = 0·004$; I^2:0 %, $P = 0·545$).

Risk of bias assessment

Inverted funnel plot analysis showed a relatively symmetrical distribution apart from an outlier (online Supplementary Figure S1) for coffee. There is a slight asymmetry for the analysis on tea (online Supplementary Figure S2). Non-parametric trim-and-fill analysis of publication bias with linear estimator showed that after the imputation of two studies, the association between tea and glioma remains significant (RR 0·81 (95 % CI 0·69, 0·95)). Egger's test showed no indication of small-study effects for both coffee ($P = 0·153$) and tea ($P = 0·730$).

Table 1. Baseline characteristics of the included studies

Authors	Study design	Region	Participants (*n*)	Cases (*n*)	Age (mean/median) years	Male (%)	Non-smoker (%)	Non-drinker (alcohol) (%)
Baglietto 2011	Prospective cohort	Australia	41 514	67	55·3	41	55·6	28·5
Burch 1986	Case–control	Southern Ontario, Canada	215 case–control pairs	42	56·9	63·7	NA	NA
Cote 2020* & Holick 2010	Prospective cohort	USA	237 516	554	44·4	21	52·4	NA
Creed 2020	Prospective cohort	UK	379 259	487	57	46·6	55·8	NA
Dubrow 2012	Prospective cohort	USA	545 771	904	62·8	59	NA	NA
Efird 2004	Retrospective cohort	USA	133 811	130	≥25	45·7	48·9	17·2
Hashibe 2015	Prospective cohort	USA	97 334	103	55–74	48·1	48	4·2
Hochberg 1990	Case–control	USA	288 (160 cases and 128 controls)	160	15–81	NA	NA	NA
Malmir 2017	Case–control	Tehran, Iran	384 (128 cases and 256 controls)	128	43	58·3	78·1	89·4
Michaud 2010	Prospective cohort	Ten European countries	410 309	343	51	34·8	44·5	NA
Nelson 2012	Prospective cohort	USA, Japanese ancestry	8006 (9 cases and 7996 control)	9	54·5	100	56·2	NA
Ogawa 2016	Prospective cohort	Japan	106 324	60	51·78	47·4	71·9	77·3

NA: not available/not reported/reported in different classification.
* Cote 2020 & Holick 2010 study was drawn from the same cohort.

Meta-regression

Meta-regression analysis was performed for cohort studies, and the relationship between coffee consumption on the risk of glioma was influenced by smoking (covariate: non-smoker, coefficient: −0·03, $P = 0·029$) (Fig. 4) and continents (North America, Europe and Asia-Pacific, $P = 0·038$), but not age (coefficient: −0·005, $P = 0·765$), male sex (coefficient: −0·004, $P = 0·579$) and alcohol consumption (covariate: non-drinker, coefficient: −0·01, $P = 0·279$). The risk reduction was greater in non-smoker and non-drinker. The most significant risk reduction occurred in the Asia-Pacific region.

Discussion

This meta-analysis showed that coffee and tea consumption was associated with a lower risk of glioma. Dose–response analysis showed a 3 % reduction in the risk of glioma for every one cup of coffee or tea per d. The dose–response was linear for the analysis on tea and potentially non-linear for the analysis on coffee.

We observed that in the pooled analysis of the highest coffee consumption *v.* the lowest, the result was borderline significant. Subgroup analysis of > 4 cups/d *v.* < 1 cup/d also showed a borderline significance with 0 % heterogeneity. However, upon sensitivity analysis, coffee was shown to reduce the risk of glioma with 0 % heterogeneity upon removal of case–control studies. This may indicate that the case–control studies introduced bias and heterogeneity to the analysis. The dose–response analysis, which excludes the case–control studies, also showed a significant risk reduction that is almost non-linear.

We performed meta-regression analysis on the cohort studies only, to reduce bias that may resulted from case–control studies. Meta-regression analysis showed that the risk reduction associated with coffee consumption was greater in non-smokers. Smoking has been shown to increase the risk of cancer, although the association is controversial in glioma[19–23]. Thus, smoking may negate the benefit of coffee consumption. Another possible confounder in the analysis was the continent where the study was located, and a greater risk reduction was found in the Asia-Pacific region. However, there is limited studies for the Asia-Pacific region as most of the studies are from North America. One of the studies that originated from Asia-Pacific was Ogawa *et al.* The author of the study acknowledged that only relatively few subjects drank coffee every day. Nevertheless, there is no indication that one study spuriously affects the RR of our pooled analysis.

Meta-analysis indicates that tea reduces the risk of glioma, and the significance remained after sensitivity analysis and subgroup analysis, indicating statistical robustness. The dose–response analysis also indicates a statistically significant risk reduction in a linear fashion. Removal of case–control studies in the sensitivity analysis results in 0 % heterogeneity. Similar to the prior analysis of coffee, case–control studies serve as the possible cause of heterogeneity in this analysis.

Funnel plot analysis was symmetrical for effect estimate related to coffee and asymmetrical for tea consumption; thus, indicating a possible publication bias related to tea consumption studies. Trim-and-fill analysis with a hypothetical imputation of the studies indicate that tea consumption will remain significant for glioma risk reduction should new studies are introduced.

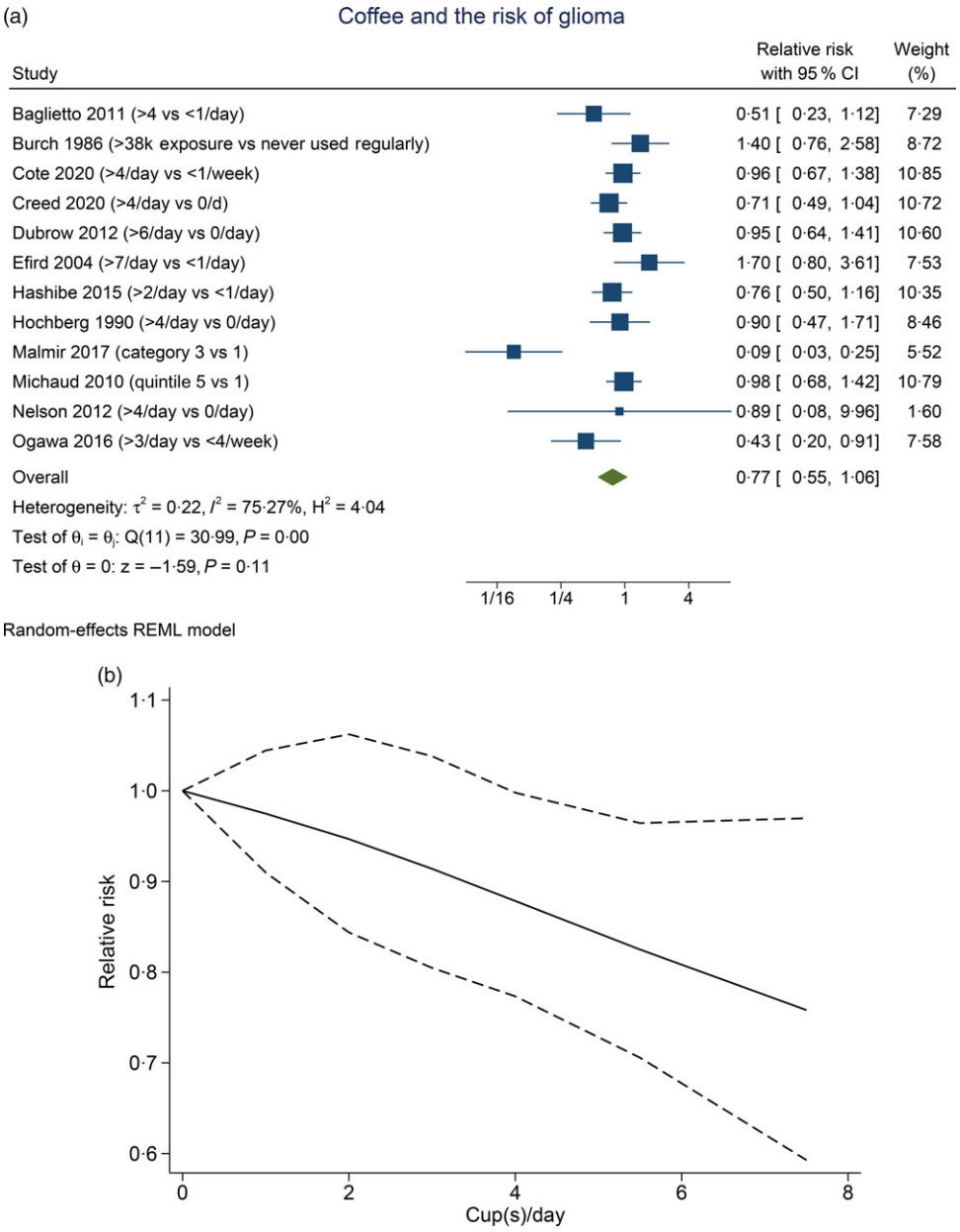

Fig. 2. Coffee and the risk of glioma. (a) Comparison between the highest *v.* lowest coffee consumption groups. (b) Dose–response meta-analysis between coffee consumption and the risk of glioma with restricted cubic splines in a multivariate random-effects dose–response model. Relative risks (solid line) with 95 % CI (long dashed lines) for the association between coffee consumption and the risk of glioma. I-squared: I^2; REML, restricted maximum likelihood.

Studies with case–control design might be biased due to psychological stress experienced by the newly diagnosed patients and the symptoms associated with the disease. This may impair the ability to recall or the willingness to fill the questionnaires. Control participants without glioma are often healthier and less stressful than patients with glioma. Prospective cohorts are less prone to bias due to data collection during a less stressful situation in terms of physical health and has a more comparable baseline. The quality of data in the cohort studies is mostly excellent and comparable to one another. However, a higher quality of data is expected in studies where source of coffee/tea data was derived from questionnaire and interview as opposed to questionnaire only. Different type of measurement may be a source of bias among the studies. Michaud *et al.* reported data from several European countries and data collection methods differed across the countries.

The follow-up length differs among the studies, which potentially contributed to heterogeneity. A comparison between exposures is often more pronounced when the events (and sample size) are higher. Also, whether the effect of coffee and tea gets stronger, stays the same or diminishes over time is unknown; thus follow-up time may affect the effect estimate. Based on the result of our analysis, heterogeneity among the cohort studies was 0 %; thus the difference in follow-up length may not contribute significantly to heterogeneity. While the others study evaluates all types of glioma, Nelson *et al.* only evaluate the

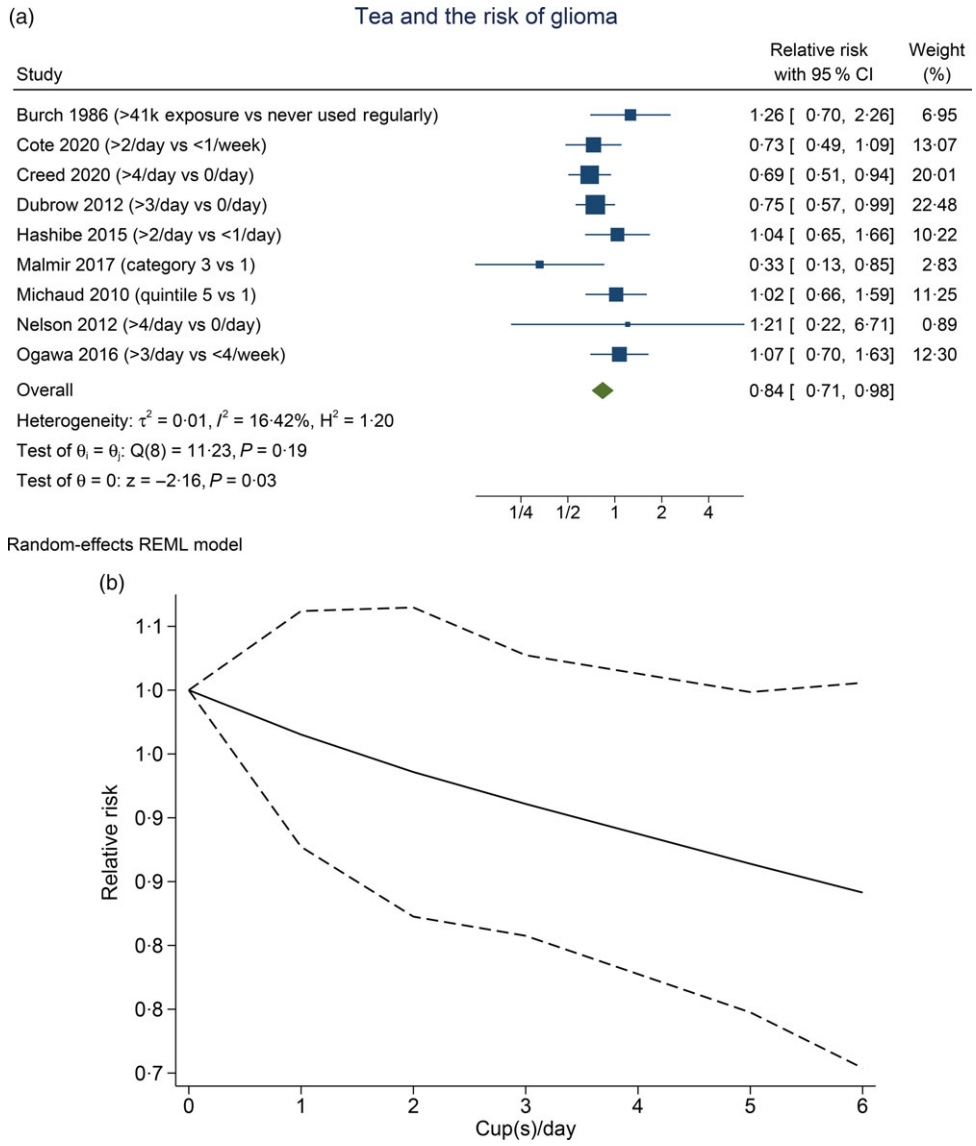

Fig. 3. Tea and the risk of glioma. (a) Comparison between the highest *v.* lowest tea consumption groups. (b) Dose–response meta-analysis between tea consumption and the risk of glioma with restricted cubic splines in a multivariate random-effects dose–response model. Relative risks (solid line) with 95 % CI (long dashed lines) for the association between tea consumption and the risk of glioma. I-squared: I^2; REML, restricted maximum likelihood.

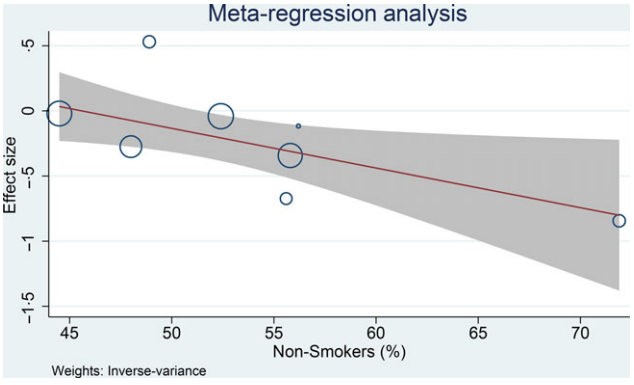

Fig. 4. Meta-regression analysis showing the association between coffee and glioma was affected by smoking. 95 %CI; studies; linear prediction.

incidence of glioblastoma. There were only nine cases in Nelson *et al.*, which may have low statistical power to detect any significant difference resulting from coffee/tea consumption.

Various therapeutic effects of polyphenols found in coffee and tea may be helpful against many pathological conditions, including cancer[5,24]. The epicatechin-3-gallate and epigallocatechin-3-gallate in tea have antiinflammation, anticarcinogenic, antiproliferative, antioxidant, antifibrosis and anticollagenase properties[25–28]. Additionally, epigallocatechin-3-gallate has been reported to reactivate methylation-silenced genes in cancer cells, including O6-methylguanine-DNA methyltransferase (MGMT)[13]. Higher MGMT activation is postulated to protect against the development of various cancers, including glioma, whereas the genetic polymorphism of MGMT has been associated with the risk of glioma[13]. Similarly, chlorogenic

Table 2. Baseline characteristics of the included studies (continued)

Authors	Outcome	Adjustment for outcome	Case ascertainment	Source of coffee/tea data	Follow-up	NOS
Baglietto 2011	Glioblastoma	None	Record linkage to the population-based Victorian Cancer Registry	FFQ	15 years	7
Burch 1986	Brain neoplasm	Multivariable logistic regression (spring water, wine, plain cigarettes, vitamin C, vitamn E, treatment for hypertension and hair dyes/hair sprays	Medical records	Questionnaire + interview	–	9
Cote 2020	Glioma	Adjusted for age, total energetic intake (quintiles), BMI (< 25 kg/m^2 *v.* 25–29·9 kg/m^2 *v.* ≥ 30 kg/m^2 *v.* missing) and smoking status (never *v.* past *v.* current *v.* missing).	Self-reported on biennial questionnaires + medical record review	FFQ	6 022 441 person years	9
Creed 2020	Glioma	Age (continuous), sex (categorical; male *v.* female), and race (categorical; non-White *v.* White) and education (categorical; completed college *v.* secondary schooling, vocational training, some college or none of the above). HR for tea were further adjusted for coffee consumption (categorical), while HR for coffee were adjusted for tea consumption (categorical).	Record linkages to the National Health Service Central Registers	UK Biobank diet survey	5·8 years	9
Dubrow 2012	Glioma	Adjusted for age, sex, race/ethnicity, energy intake, height, fruit and vegetable intake, and nitrite intake from plant sources	Probabilistic linkage with state cancer registries	FFQ	10·6 years	9
Efird 2004	Malignant primary adult-onset glioma	Adjusted for cigarettes, cigars, pipes, sex, race, education, alcohol and coffee.	Kaiser Permanente Medical Care Program of Northern California Registry	Self-administered questionnaire	21 years (maximum), 13·2 +/– 6·7 years (mean)	9
Hashibe 2015	Glioma	Unadjusted	Annual study update was used to ascertain cancer diagnoses and was mailed annually to the study participants	Diet History Questionnaire	–	8
Hochberg 1990	Glioma	Age-adjusted	Newly diagnosed patients	Questionnaire	–	6
Malmir 2017	Glioma	Model 2: further adjustments were made for physical activity, family history of cancers, family history of glioma, marital status, education, high-risk occupation, high-risk residential area, duration of cell phone use, supplement use, history of exposure to the radiographic X-ray, history of head trauma, history of allergy, history of hypertension, smoking status, exposure to chemicals, drug use, personal hair dye, frequent fried food intake, frequent use of barbecue, canned foods and microwave. Model 3: additionally, adjusted for meats and processed meats, legumes and nuts, fruits, salt, and interaction effects of tea and coffee consumption. Model 4: further adjusted for BMI.	Newly diagnosed patients (< 1 month)	FFQ	–	7
Michaud 2010	Glioma and meningioma	Adjusted for smoking status, BMI and education.	Combination of health insurance records and cancer and mortality registries.	FFQ + interview (Sweden)	8·5 years	9
Nelson 2012	Glioblastoma multiforme	Unadjusted	Searching the entire cohort database for the years 1965–1998 using International Classification of Diseases (ICD 9) codes for oncology + manual review by an author	Questionnaire + 24-h recall interviews + 7-d dietary records (2 years later)	Follow-up over 30-year period among 8006 men	8
Ogawa 2016	Brain tumours	Adjusted for age, sex, BMI, pack-years of cigarettes (never and past, 0–20 years, > 20 years), alcohol intake (non-, past and 1–3 times/month drinker, 150 g of ethanol per week), coffee (4 d/week, 1–2 cups/d, 3 cups/d), past history of allergy and past history of diabetes mellitus.	Records of major local hospitals and population-based cancer registries.	Self-administered questionnaire	18·1 years	9

HR: Hazard Ratio, FFQ: Food Frequency Questionnaire, NOS: Newcastle–Ottawa Scale.

acid, a polyphenol found in coffee, has antioxidative and antibacterial properties, as well as anticarcinogenic roles via 5' adenosine monophosphate- activated protein kinase (AMPK) activation[12].

Coffee and tea also contain methylxanthines (e.g. theophylline and caffeine) which have anti-inflammatory action and allow enhancement of cerebrospinal fluid production[29]. These small lipophilic molecules can cross the blood–brain barrier to encourage clearing or diluting of neurotoxins, thereby reducing the risk of glioma[4]. However, the effect on cancer progression may vary given the wide variety of brewing method and different types of coffee and tea[30].

Specific brewing techniques can affect the concentration of certain substances found in coffee and tea, including caffeine[6]. For instance, 1 liquid oz (29·6 ml) of espresso obtained from pressurised brewing method contains 64 mg of caffeine, while 8 liquid oz (236·6 ml) of gravity-brewed coffee (e.g. filtered coffee) contains 96 mg of caffeine[31]. Variability inevitably leads to measurement errors, and total volume consumed per d may not reflect the actual consumption of compounds contained in coffee and tea accurately[13]. Previous study showed that filtered brew was associated with reduced any cause of mortality compared with unfiltered brew and no coffee consumption[32]. Nevertheless, there is currently no evidence that indicate a specific type of brewing method influence the risk of glioma differently[6].

Depending on the experimental condition, caffeine may facilitate and limit the development of malignant cells by reducing cerebral blood flow and eventually restricting access to oxygen and nutrients, thereby inhibiting angiogenesis and carcinogenesis[6,33–35]. With regard to glioblastoma, caffeine has been reported to decelerate the growth and invasion of glioblastoma and consequently prolong survival by inhibiting Ca release channel[36], reducing hypoxia-inducible factors (HIF)-1α and vascular endothelium growth factor expression in glioblastoma cells[37], reducing the invasion of glioma cells from different signalling pathways[38,39] and promoting forkhead box protein O1 (FoxO1)-Bim-mediated cell apoptosis[40].

One of the limitations encountered in the present study is that we were unable to provide subset analysis on types of coffee and teas, and other specifics such as filtered or decaffeinated coffee because most of studies did not report it. Also individuals may also switch their types of coffee over time. Analysis of the cross-sectional studies might not be fully accurate due to recall bias; nevertheless, most of the studies were cohort. The source of data collection varies among the studies (i.e. FFQ, other questionnaire, with or without interviews, etc). Additionally, numerous confounders are present in the observational studies on lifestyle, and these confounders might not be adequately reported and adjusted. The significant summary measures in the present study were very much driven by a small number of studies. Thus, additional large and high-quality prospective cohorts are required before definite conclusion.

Conclusion

This meta-analysis showed that there is an apparent association between coffee and tea intake and risk of glioma.

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R. P. conceived and designed the study and drafted the manuscript. R. P. and M. A. L. acquired the data and drafted the manuscript. J. H., A. F., R. P. and J. J. performed data extraction, interpreted the data and performed extensive research on the topic. R. P., R. V., A. F. and M. A. L. drafted the initial manuscript. R. P., R. V., N. G. and J. J. reviewed and performed extensive editing of the manuscript. R. P. performed the statistical analysis. All authors contributed significantly to the writing of the manuscript. All authors approve the final manuscript.

The authors declare that they have no competing interests.

Supplementary material

For supplementary material referred to in this article, please visit https://doi.org/10.1017/S0007114521000830

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