Original Research

A prospective study of coffee and tea consumption and the risk of glioma in the UK Biobank

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Abstract   *Background:* Coffee and tea have been hypothesised to reduce the risk of some cancers; however, their impact on glioma is less well studied.
Methods: We examined associations between self-reported intake of tea and coffee in relation to glioma risk in the UK Biobank. We identified 487 incident glioma cases among 379,259 participants. Hazard ratios (HR) and 95% confidence intervals (CI) for glioma according to caffeinated beverage consumption were calculated using Cox proportional hazards regression with adjustment for age, gender, race and education; daily cups of tea or coffee were included in models considering the other beverage.
Results: Consuming 4 or more cups of tea was associated with reduced risk of glioma when compared to no tea consumption (HR = 0.69; 95% CI, 0.51−0.94). A significant inverse association was observed for glioblastoma (HR = 0.93 per 1 cup/d increment; 95% CI, 0.89−0.98) and among males for all gliomas combined (HR = 0.95 per 1 cup/d increment; 95% CI, 0.90−1.00). A suggestive inverse association was also observed with greater consumption of coffee (HR = 0.71; 95% CI, 0.49−1.05 for >4 versus 0 cups/d). Results were not materially changed with further adjustment for smoking, alcohol and body mass index. Associations were similar in 2-year and 3-year lagged analyses.

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Conclusions: In this prospective study, we found a significant inverse association between tea consumption and the risk of developing glioma, and a suggestive inverse association for the consumption of coffee. Further investigation on the possible preventive role of caffeine in glioma is warranted.

1. Introduction

Glioma is a devastating tumour of the central nervous system. Tumours arise from glial cells of the brain and represent approximately 80% of adult malignant brain tumours [1]. The few established risk factors include older age, male gender and European ancestry, as well as atopy/allergic conditions [2] and ionising radiation from medical and environmental exposures [3]. The role of diet and modifiable lifestyle-related factors remains poorly studied.

Diverse health benefits have been ascribed to coffee and tea, the most frequently consumed beverages in the world, including reductions in neurodegenerative diseases [4−6] and several cancers [7−10]. Coffee and tea are rich in polyphenol compounds which have antioxidant properties [11] although the types of polyphenols differ in coffee and tea: coffee is rich in phenolic acids, whereas tea is rich in flavonoids [12]. Both beverages contain methylxanthines including caffeine (1,3,7-trimethylxanthine; found predominantly in coffee) and theophylline (1,3-dimethylxanthine; found predominantly in tea). All methylxanthines are small lipophylic molecules that readily cross the blood−brain barrier [13,14]. Methylxanthines may have anti-inflammatory effects [15] and have been shown to increase production of cerebrospinal fluid [16] and thus may promote clearance or dilution of neurotoxins, thereby decreasing glioma risk. Furthermore, caffeine specifically has many physiological effects on the brain by blocking the receptor of the neurotransmitter adenosine [17,18] which may protect against excitotoxic or ischemic neuronal injury [19].

Whether coffee or tea alters risk of glioma has not been established. Five case−control studies [20−24] and 6 prospective cohorts [25−32] have reported on caffeinated beverages with mixed results, whereas individual cohort studies have reported inverse associations with coffee [29,31], tea [28,32] or tea and coffee considered together [27,28]; a recent pooled analysis [30] of 3 cohorts (the UK Million Women Study and 2 of the previously studied cohorts, the Prostate, Lung, Colorectal and Ovarian [PLCO] Cancer Screening Trial [31] and the NIH-AARP Diet and Health study [28] including 1.2 million participants and 2313 glioma cases, reported no significant associations for coffee or tea consumption with glioma risk.

In this report, we examine the association of coffee and tea consumption with glioma incidence based on an analysis from the UK Biobank [33,34].

2. Participants and methods

2.1. UK Biobank

This analysis was conducted in an established population-based cohort, the UK Biobank [33,34]. This cohort follows approximately 500,000 individuals from the UK who were 40−69 years old at the time of recruitment in 2006−2010. Prospective participants for the cohort were initially identified from National Health Service patient registries and then were invited to complete a baseline questionnaire at one of the 22 recruitment assessment centres. All participants of the UK Biobank provided written consent at recruitment.

Coffee and tea consumption were collected at baseline as part of the UKB diet survey, where participants were asked 'How many cups of tea do you drink each day? (Include black and green tea)' (UKB Data-field ID: 1488) and 'How many cups of coffee do you drink daily?' (UKB Data-field ID: 1498), with open-ended responses to both questions. The type of coffee considered included decaffeinated coffee, instant coffee, ground coffee and any other type of coffee (UKB Data-field ID: 1508). A variable for total coffee and tea consumption was created by additively combining daily cups of tea and coffee into a single measure.

Participants were followed through ongoing record linkages to the National Health Service Central Registers which provide information on cancer diagnoses coded according to the World Health Organisation International Classification of Diseases (ICD) [35]. Incident primary intracranial gliomas (ICD10: C71) were comprised of glioblastomas (GBM) (9440−9441) or lower-grade glioma subtypes ([non-GBM]; 9382, 9400−9401, 9410−9411, 9420, 9424−9425, 9450−9451).

2.2. Statistical analysis

Of the 502,536 participants in the UK Biobank, we excluded those with a history of any cancer at recruitment as well as any genetically related participants, leaving 380,791 participants for analysis. An additional 1532 participants were excluded because they did not

report coffee or tea consumption at baseline, leaving 379,259 participants for the present analysis spanning 807,218,131 recorded person-years. We calculated hazard ratios (HR) and 95% confidence intervals (CI) for glioma for tea, all coffee, caffeinated coffee, and tea and coffee combined, using Cox proportional hazards regression. (Numbers of glioma cases reporting instant coffee (n = 206), ground (n = 87) and decaffeinated (n = 76) were too limited for separate analysis.) Cups of coffee and tea per day were treated first as categorical variables in analyses and modelled as 0, >0−2, >2−4 and >4 cups per day. For evaluation of the combination of coffee and tea consumption, the highest category was expanded to include >4−6 and >6 cups per day. All models were adjusted for age (continuous), gender, race (white versus non-white) and education (secondary schooling, vocational training, some college, completed college or none of the above). Smoking status (never, previous or current), alcohol consumption (continuous) and body mass index (BMI) (kg/m^2) (continuous) were also considered as potential confounders. The number of cups of coffee and tea consumed each day were negatively correlated (Pearson r = −0.25, overall; Pearson r = −0.23, in men; and r = −0.28, in women); therefore, daily cups of tea or coffee consumed were included in models considering the other beverage. Analysis of linear trends was also conducted for each beverage. Follow-up time constituted the time from enrolment to diagnosis of glioma or another cancer, death, or last linkage. Analyses were performed for all gliomas and by glioma subtype (e.g. glioblastoma and lower-grade gliomas) overall, and by gender. To evaluate potential effects of protopathic bias on results, we further conducted lagged analyses that initiated follow-up at two years or three years following baseline assessment of coffee and tea intake.

A p-value less than 0.05 was considered statistically significant. Analyses were performed using R (version 3.5.0).

3. Results

The 379,259 participants were followed for a median of 5.8 years after enrolment, with 2,201,249 recorded person-years. A total of 487 glioma cases (364 glioblastomas and 123 lower-grade gliomas) were diagnosed a median of 3.8 years after enrolment (range, 0.3 months−9.0 years). The present analyses were based on 470 glioma cases that completed questions on their intake of tea and 453 glioma cases that reported their intake of coffee. Glioma cases were older and more likely to be male and White than non-cases (Table 1). Median intake of tea among cohort participants was 3 cups per day (interquartile range [IQR], 2−5 cups), and the median intake of all coffee types combined was 2 cups per day (IQR, 1−3 cups). The great majority of

cohort members reported regular consumption of one of these caffeinated beverages. (A total of 10 glioma cases and 9076 total participants reported neither coffee nor tea consumption.)

When compared to no consumption, glioma incidence was approximately 30% lower with intake of greater than 4 cups per day of tea (HR = 0.69; 95% CI, 0.51−0.94) and coffee (HR = 0.71; 95% CI, 0.49−1.05), although only the association for tea consumption was statistically significant (Fig. 1). When considering extreme levels of consumption (not shown), inverse associations were more pronounced for consumption of greater than 8 cups per day of tea (HR = 0.43; 95% CI, 0.21−0.86) and coffee (HR = 0.39; 95% CI, 0.09−1.59), although results were based on few glioma cases (n = 14 and n = 3, respectively) that reported this level of consumption.

When intake was modelled continuously (HR for an increment of 1 cup/day), for all gliomas combined, inverse associations were observed with tea (HR = 0.96; 95% CI, 0.92−1.00), all coffee (HR = 0.96; 95% CI, 0.91−1.01), and tea and coffee combined (HR = 0.97; 95% CI, 0.93−1.00).

For glioblastoma, a significant trend of lower risk was observed with increasing cups of tea consumed per day (p trend = 0.003): those reporting more than 4 cups per day had a 45% reduced risk (HR = 0.55; 95% CI, 0.38−0.79) when compared to non-tea drinkers (Table 2). Consumption of all coffee types was suggestively associated with a reduced risk (p trend = 0.09), and, in combination, increasing consumption of tea and coffee was associated with a significant reduction in glioblastoma risk (p trend = 0.01).

For lower-grade glioma, no significant trends were observed with increasing consumption of tea (p trend = 0.36), all coffee (p trend = 0.60), caffeinated coffee (p trend = 0.60) or tea and coffee combined (p trend = 0.79).

When considered by gender (Table 3), significant inverse associations were observed for the consumption of tea among men (299 glioma cases); drinking more than 4 cups of tea per day (based on 80 exposed cases) was associated with a ∼40% reduction in glioma risk (HR = 0.59; 95% CI, 0.40−0.88) compared to men who reported no tea consumption. A suggestive inverse association was also observed with greater consumption of coffee (HR comparing >4 versus 0 cups/day: 0.67 [95% CI, 0.43−1.06]), and the combination of coffee and tea was associated with a suggestive inverse association among men. Among women (188 glioma cases), neither coffee nor tea, individually or in combination, was associated with glioma risk (p trend > 0.3) although HR of less than 1 were observed for all levels of tea consumption when compared to no tea consumption.

All results for tea and coffee were essentially unchanged in both the 2-year and 3-year lagged analysis with statistically significant inverse associations

Table 1
Descriptive summary of UK Biobank participants by baseline coffee and/or tea consumption.

	Tea (cups/day)				Coffee (cups/day)				Tea or coffee (cups/day)			
	0	>0–2	>2-4	>4	0	>0–2	>2-4	>4	0–2	>2-4	>4-6	>6
Total number	56,084	87,796	110,560	113,099	84,679	146,648	78,147	42,303	48,296	103,759	124,589	102,128
Glioma cases	83	103	144	140	107	189	106	51	65	133	161	128
Age at enrolment, years												
Median	55	56	58	57	55	58	57	56	54	57	58	57
IQR	48−62	48−62	50−63	50−63	48−62	50−63	50−63	49−62	46−61	49−63	50−63	50−63
Gender												
Male, n (%)	25,375 (45%)	42,339 (48%)	50,049 (45%)	53,344 (47%)	36,111 (43%)	66,279 (45%)	38,910 (50%)	23,052 (54%)	20,616 (43%)	46,779 (45%)	57,518 (46%)	51,775 (51%)
Female, n (%)	30,792 (55%)	45,560 (52%)	60,655 (55%)	59,895 (53%)	48,675 (57%)	80,558 (55%)	39,343 (50%)	19,302 (46%)	27,745 (57%)	57,113 (55%)	67,232 (54%)	50,481 (49%)
Race												
White, n (%)	53,225 (95%)	78,836 (90%)	103,399 (93%)	109,227 (97%)	75,210 (89%)	138,246 (94%)	75,754 (97%)	4192 (98%)	40,384 (84%)	95,538 (92%)	120,003 (96%)	99,312 (97%)
Non-white, n (%)	2718 (5%)	8728 (10%)	6972 (6%)	3655 (3%)	9259 (11%)	8121 (6%)	2227 (3%)	908 (2%)	7733 (16%)	7988 (8%)	4393 (4%)	2594 (3%)
Education												
Secondary schooling, n (%)	16,327 (29%)	22,747 (26%)	29,443 (27%)	30,520 (27%)	24,182 (29%)	37,726 (26%)	20,439 (26%)	12,104 (29%)	12,837 (27%)	27,647 (27%)	33,631 (27%)	27,417 (27%)
Vocational training, n (%)	2792 (5%)	4119 (5%)	5695 (5%)	5964 (5%)	4137 (5%)	7584 (5%)	3989 (5%)	2083 (5%)	2228 (5%)	5066 (5%)	6394 (5%)	5374 (5%)
Some college, n (%)	10,311 (18%)	15,572 (18%)	19,331 (18%)	20,502 (18%)	15,033 (18%)	26,051 (18%)	13,094 (18%)	7800 (18%)	8699 (18%)	18,202 (18%)	22,442 (18%)	18,411 (18%)
Completed college, n (%)	17,430 (31%)	32,987 (38%)	37,112 (34%)	33,521 (30%)	23,428 (28%)	52,040 (35%)	28,311 (36%)	12,867 (30%)	17,234 (36%)	35,998 (35%)	41,220 (33%)	31,638 (31%)
None of the above, n (%)	8759 (16%)	11,368 (13%)	17,835 (16%)	21,473 (19%)	16,725 (20%)	21,895 (15%)	10,914 (14%)	7057 (17%)	6605 (14%)	15,772 (15%)	19,804 (16%)	18,340 (18%)
Smoking status												
Never, n (%)	29,956 (53%)	49,981 (57%)	64,034 (58%)	61,396 (54%)	50,908 (60%)	84,234 (58%)	41,672 (53%)	18,466 (44%)	30,309 (63%)	60,346 (58%)	69,621 (56%)	51,032 (50%)
Previous, n (%)	18,648 (33%)	29,439 (34%)	37,568 (34%)	38,047 (34%)	25,545 (30%)	50,407 (34%)	27,918 (36%)	14,979 (35%)	14,122 (29%)	35,094 (34%)	43,206 (35%)	35,078 (34%)
Current, n (%)	7399 (13%)	8168 (9%)	8705 (8%)	13,359 (12%)	8006 (9%)	11,721 (8%)	8386 (11%)	8759 (21%)	3743 (8%)	8085 (8%)	11,528 (9%)	15,739 (15%)
Body mass index												
Median	27.36	26.60	26.5	26.72	26.74	26.42	26.93	27.55	26.67	26.58	26.65	26.96
IQR	24.46−30.86	24.02−29.70	24.00−29.56	24.17−29.81	24.02−30.06	23.91−29.47	24.41−30.01	24.84−30.74	23.81−30.15	23.98−29.76	24.16−29.74	24.36−30.01
Number of drinks (weekly)												
Median	5	6	6	5	3	6	7	6	4	6	6	6
IQR	0−12	0−12	0−12	0−11	0−10	0−12	1−13	0−13	0−10	0−12	0−12	0−12

IQR, interquartile range.
Cohort size and number of incident gliomas vary between exposures due to the number of participants who skipped questions on tea only or coffee only. Data were missing for smoking in 1356 subjects (0.36% of the cohort; 4 glioma cases), for body mass index in 1505 subjects (0.40% of the cohort; 1 glioma case) and for consumption of alcohol in 330 subjects (0.09% of the cohort; 1 glioma case).
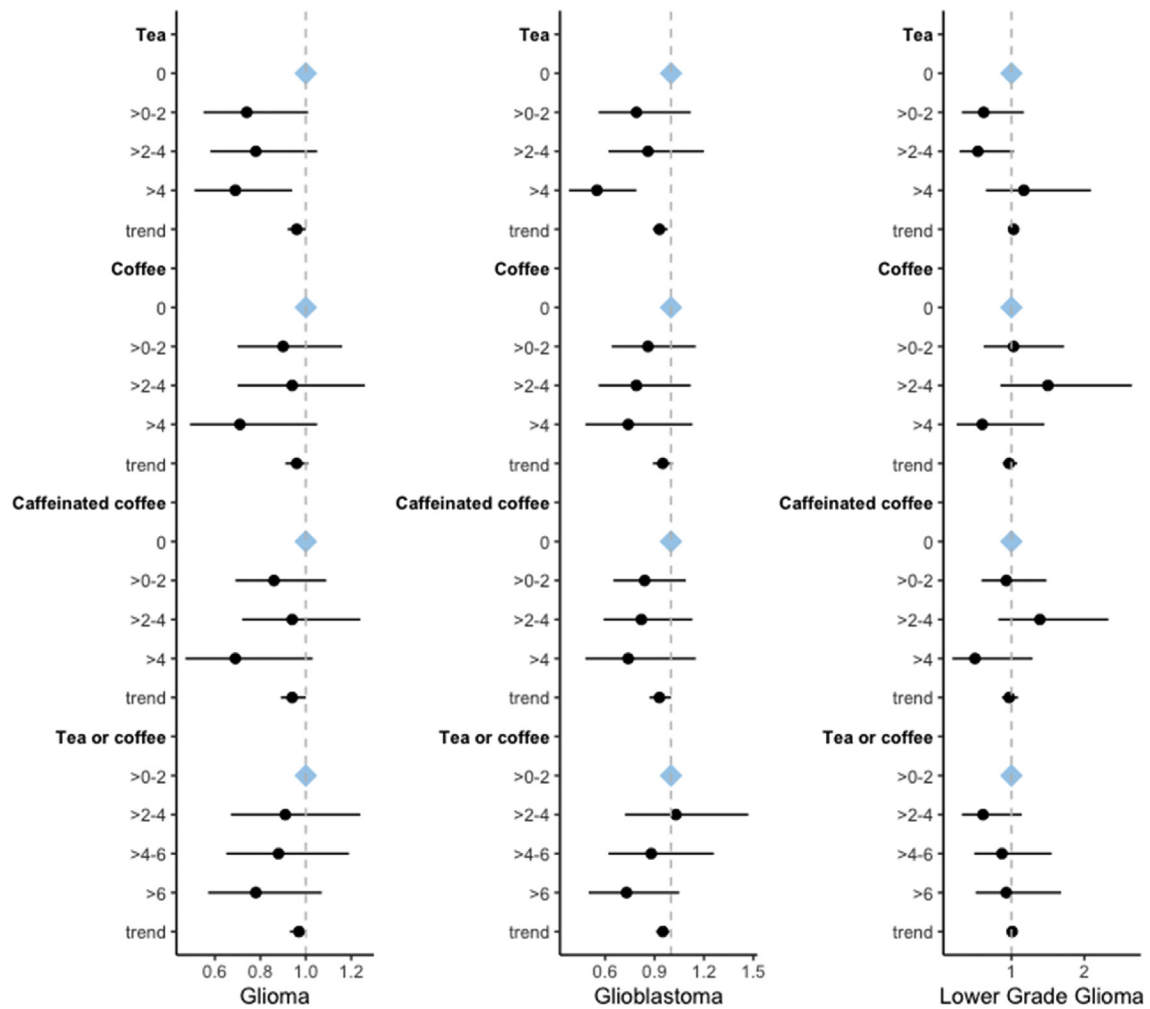
Fig. 1. Summary of hazard ratios and 95% confidence intervals (*x*-axis) for cups per day categories and linear trend for tea, all coffee types, caffeinated coffee, and tea and coffee combined for all gliomas combined, glioblastoma and lower-grade glioma. Hatched vertical line indicates the null reference value of '1'.

observed with increasing tea consumption for all gliomas and glioblastomas only in both genders combined regardless of lag period, and with significant findings for all gliomas among males but not females (Supplemental Tables 1 and 2).

We further considered potential confounding of the tea and coffee associations by smoking habits, alcohol consumption, and BMI. Neither smoking status, total weekly alcohol drinks, nor BMI were associated with glioma risk in these data (not shown). Among current smokers, cups of both coffee and tea consumed per day were positively correlated with the number of cigarettes smoked per day (Pearson r = 0.16 and 0.10, respectively). Alcohol consumption was only weakly associated with consumption of coffee and tea (Pearson r = 0.07 and −0.03, respectively); BMI was weakly correlated with coffee and tea intake (Pearson r = 0.05 and −0.02, respectively). When smoking status, weekly alcohol consumption and BMI were included in multivariable models, associations of tea and coffee intake with glioma risk were essentially unchanged (Supplemental Table 3).

4. Discussion

In this prospective cohort study based on the UK Biobank, we examined the relationship of coffee and tea consumption with the subsequent development of glioma. We observed inverse associations with increasing consumption of tea that were statistically significant for all gliomas combined, and when restricting to glioblastoma and men. Results were independent of smoking habits, BMI and the amount of alcohol or coffee consumed. Findings were also consistent with a protective association with greater consumption of coffee although these results were based on fewer coffee drinkers and results were non-significant. Coffee and tea consumption in combination was associated with a reduced glioma risk.

Table 2
Coffee and tea consumption in relation to glioma risk: UK Biobank.

	All gliomas			Glioblastoma			Lower-grade glioma		
	# Gliomas	HR (95% CI)[a]	P value	# Glioblastomas	HR (95% CI)[a]	P value	# Lower-grade gliomas	HR (95% CI)[a]	P value
Tea (cups/day)									
0	83	Ref		62	Ref		21	Ref	
>0-2	103	0.74 (0.55−1.01)	0.06	83	0.79 (0.56−1.12)	0.18	20	0.62 (0.32−1.17)	0.14
>2-4	144	0.78 (0.58−1.05)	0.10	117	0.86 (0.62−1.20)	0.37	27	0.54 (0.29−1.03)	0.06
>4	140	0.69 (0.51−0.94)	0.02	90	0.55 (0.38−0.79)	0.001	50	1.17 (0.65−2.09)	0.60
Test for trend (cups/day)	470	0.96 (0.92−1.00)	0.04	352	0.93 (0.89−0.98)	0.003	118	1.03 (0.97−1.09)	0.36
Coffee − all (cups/day)									
0	107	Ref		80	Ref		27	Ref	
>0-2	189	0.90 (0.70−1.16)	0.41	144	0.86 (0.64−1.15)	0.30	45	1.03 (0.62−1.72)	0.91
>2-4	106	0.94 (0.70−1.26)	0.66	74	0.79 (0.56−1.12)	0.18	32	1.50 (0.85−2.65)	0.16
>4	51	0.71 (0.49−1.05)	0.08	43	0.74 (0.48−1.13)	0.16	8	0.60 (0.25−1.45)	0.25
Test for trend (cups/day)	453	0.96 (0.91−1.01)	0.10	341	0.95 (0.89−1.01)	0.09	112	0.97 (0.88−1.08)	0.60
Coffee − caffeinated only (cups/day)[b]									
0	176	Ref		131	Ref		45	Ref	
>0-2	147	0.86 (0.69−1.09)	0.21	112	0.84 (0.65−1.09)	0.20	35	0.93 (0.59−1.48)	0.76
>2-4	86	0.94 (0.72−1.24)	0.67	60	0.82 (0.59−1.13)	0.23	26	1.39 (0.82−2.33)	0.22
>4	40	0.69 (0.47−1.03)	0.07	34	0.74 (0.48−1.15)	0.18	6	0.50 (0.19−1.29)	0.15
Test for trend (cups/day)	449	0.94 (0.89−1.00)	0.06	337	0.93 (0.87−1.00)	0.04	112	0.97 (0.87−1.09)	0.60
Tea or coffee (cups/day)									
0−2	65	Ref		48	Ref		17	Ref	
>2-4	133	0.91 (0.67−1.24)	0.56	109	1.03 (0.72−1.47)	0.88	24	0.61 (0.32−1.14)	0.12
>4-6	161	0.88 (0.65−1.19)	0.39	117	0.88 (0.62−1.26)	0.48	44	0.87 (0.49−1.55)	0.64
>6	128	0.78 (0.57−1.07)	0.12	90	0.73 (0.50−1.05)	0.09	38	0.93 (0.51−1.68)	0.81
Test for trend (cups/day)	487	0.97 (0.93−1.00)	0.04	364	0.95 (0.91−0.99)	0.01	123	1.01 (0.95−1.07)	0.79

[a] Hazard ratios (HR) and 95% confidence interval (CI) adjusted for age (continuous), gender (categorical; male versus female), race (categorical; non-white versus white) and education (categorical; completed college versus secondary schooling, vocational training, some college or none of the above). HRs for tea were further adjusted for coffee consumption (categorical), while HRs for coffee were adjusted for tea consumption (categorical).

[b] Includes ground (including espresso); instant or 'other' types of coffee.

The present findings are consistent with several though not all prospective studies on the association of coffee or tea intake with glioma risk. In an analysis based on the Kaiser Permanente Medical Care Program of Northern California [25] and 130 incident gliomas, coffee consumption was associated with a suggestive dose-dependent increase in risk although all results were imprecise; results for tea consumption were not reported. A recent report [32] from the Nurses' Health Study and the Health Professionals Follow-Up Study, based on 554 cases, found a marginally significant inverse association for the consumption of tea, but not coffee, similar to the present study. An inverse association of glioma with coffee and tea consumption combined was supported in a study based in the EPIC which spans 10 European countries [27]. Initial results from the PLCO cohort [31] suggested an inverse association with coffee consumption in men, and a report from the NIH-AARP Diet and Health Study [28] suggested a borderline inverse association with consumption of high levels of tea, or coffee and tea combined. However, a recent pooled analysis [30] that included these two cohorts and the Million Women Study (with a total of 2313 glioma cases) reported no significant associations for coffee and/or tea intake with glioma risk, or in any of the 3 individual cohort studies. The Japan Public Health Center-Based Prospective Study [29] reported a nonsignificant inverse association for coffee and no association with green tea consumption, although this study had only 60 incident glioma cases. The reasons for these disparate results across studies is not clear but may be due to differences in average coffee and/or tea consumption levels in the study populations, imprecision due to low case numbers in some studies, or differences by sex, follow-up time, or composition of the glioma case group. (In the present study, inverse associations were observed mainly for glioblastoma and among men.)

Strengths of the present analysis include the large size of the UK Biobank cohort and the appreciable numbers of incident glioma cases that allowed for a reasonably powerful test of the association between coffee and tea

Table 3
Coffee and tea consumption in relation to glioma risk according to sex: UK Biobank.

	All gliomas - males			All gliomas - females		
	# Gliomas	HR (95% CI)[a]	P value	# Gliomas	HR (95% CI)[a]	P value
Tea (cups/day)						
0	52	ref		31	ref	
>0−2	68	0.77 (0.52−1.12)	0.17	35	0.67 (0.40−1.13)	0.13
>2−4	91	0.80 (0.55−1.16)	0.23	53	0.70 (0.43−1.14)	0.16
>4	80	0.59 (0.40−0.88)	0.009	60	0.84 (0.51−1.38)	0.49
test for trend (cups/day)	291	0.95 (0.90−1.00)	0.04	179	0.97 (0.91−1.04)	0.40
Coffee - all (cups/day)						
0	73	ref		34	ref	
>0−2	110	0.77 (0.56−1.06)	0.11	79	1.15 (0.75−1.75)	0.53
>2−4	64	0.78 (0.54−1.12)	0.17	42	1.26 (0.77−2.07)	0.36
>4	36	0.67 (0.43−1.06)	0.09	15	0.70 (0.34−1.43)	0.32
test for trend (cups/day)	283	0.95 (0.90−1.02)	0.16	170	0.95 (0.87−1.05)	0.31
Coffee - caffeinated only (cups/day)[b]						
0	107	ref		69	ref	
>0−2	88	0.80 (0.59−1.07)	0.13	59	0.98 (0.68−1.41)	0.89
>2−4	56	0.87 (0.62−1.23)	0.44	30	1.05 (0.66−1.66)	0.85
>4	30	0.71 (0.45−1.12)	0.14	10	0.57 (0.26−1.28)	0.17
test for trend (cups/day)	281	0.94 (0.87−1.01)	0.07	168	0.96 (0.86−1.06)	0.41
Tea or coffee (cups/day)						
0−2	40	ref		25	ref	
>2−4	84	0.91 (0.61−1.36)	0.66	49	0.88 (0.53−1.44)	0.61
>4−6	89	0.77 (0.52−1.14)	0.19	72	1.01 (0.63−1.61)	0.98
>6	86	0.78 (0.52−1.16)	0.22	42	0.73 (0.44−1.24)	0.25
test for trend (cups/day)	299	0.96 (0.92−1.00)	0.06	188	0.97 (0.92−1.03)	0.34

[a] Hazard ratios (HR) and 95% confidence interval (CI) adjusted for age (continuous), gender (categorical; male versus female), race (categorical; non-white versus white) and education (categorical; completed college versus secondary schooling, vocational training, some college or none of the above). HRs for tea were further adjusted for coffee consumption (categorical), while HRs for coffee were adjusted for tea consumption (categorical).

[b] Includes ground (including espresso); instant or 'other' type of coffee.

consumption and the risk of glioma. Furthermore, the high prevalence of tea consumption in this cohort (as opposed to US-based cohorts) provided an opportunity to study a wide range of exposure, and results suggest greatest risk reduction in those consuming more than 4 cups per day. However, several limitations should be noted. Follow-up in the UK Biobank is relatively limited (participants were followed a median of 5.8 years), raising the possibility that reverse causation may have affected results (i.e. glioma cases with preclinical symptoms may have altered their intake of caffeinated beverages); however, given that the magnitude of inverse associations for both tea and coffee consumption in relation to glioma and glioblastoma was similar after excluding the first 2 or 3 years of observation, such bias is unlikely to explain the current findings. The study had limited power to detect associations in stratified analyses, especially restricting to lower-grade gliomas that comprised only 25% of the glioma cases. The study was also composed of predominantly Caucasians, limiting the generalisability of the results to other racial/ethnic groups that may have different consumption patterns. It was also not possible to define an unexposed referent group in analyses of coffee and tea consumption combined as virtually the entire cohort reported regular consumption of coffee, tea or both beverages. Measures

of tea and coffee consumption after baseline assessment were only available for a small subset of participants (approximately 4%) and we were unable to examine changes in consumption over time or to identify occasional drinkers over the course of follow-up. Finally, as participants were asked to report usual daily coffee and tea consumption, some persons in the referent group may have been occasional drinkers of these beverages.

5. Conclusion

In this prospective cohort study, we found an inverse association between tea consumption and the risk of developing glioma, with a suggestive inverse association also observed with the consumption of coffee. Further investigation on the possible preventive role of caffeine in glioma is warranted.

Author contributions

K.M.E. designed and directed research; J.H.C., T.A.G. and K.M.E. acquired data; J.H.C., T.A.G. and K.M.E. analysed and interpreted data; J.H.C. and K.M.E. wrote the paper; and S.S.W. and T.A.G. provided critical revision of the manuscript for intellectual content.

Funding

Conflict of interest statement

The authors declare that they have no conflict of interest.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Data availability

The datasets analysed during the present study are available from the UK Biobank with an approved protocol.

Acknowledgement

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2020.01.012.

References

[1] Ostrom QT, Gittleman H, Liao P, Vecchione-Koval T, Wolinsky Y, Kruchko C, et al. CBTRUS Statistical Report: primary brain and other central nervous system tumors diagnosed in the United States in 2010-2014. Neuro Oncol 2017;19:v1−88.

[2] Amirian ES, Zhou R, Wrensch MR, Olson SH, Scheurer ME, Il'yasova D, et al. Approaching a scientific consensus on the association between allergies and glioma risk: a report from the glioma international case-control study. Cancer Epidemiol Biomark Prev 2016;25:282−90. a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology.

[3] Braganza MZ, Kitahara CM, Berrington de Gonzalez A, Inskip PD, Johnson KJ, Rajaraman P. Ionizing radiation and the risk of brain and central nervous system tumors: a systematic review. Neuro Oncol 2012;14:1316−24.

[4] Costa J, Lunet N, Santos C, Santos J, Vaz-Carneiro A. Caffeine exposure and the risk of Parkinson's disease: a systematic review and meta-analysis of observational studies. J Alzheimers Dis 2010;20(Suppl 1):S221−38.

[5] Santos C, Costa J, Santos J, Vaz-Carneiro A, Lunet N. Caffeine intake and dementia: systematic review and meta-analysis. J Alzheimers Dis 2010;20(Suppl 1):S187−204.

[6] Chen JF, Chern Y. Impacts of methylxanthines and adenosine receptors on neurodegeneration: human and experimental studies. Handb Exp Pharmacol 2011:267−310.

[7] Cao S, Liu L, Yin X, Wang Y, Liu J, Lu Z. Coffee consumption and risk of prostate cancer: a meta-analysis of prospective cohort studies. Carcinogenesis 2014;35:256−61.

[8] Zhou Q, Luo ML, Li H, Li M, Zhou JG. Coffee consumption and risk of endometrial cancer: a dose-response meta-analysis of prospective cohort studies. Sci Rep 2015;5:13410.

[9] Bravi F, Tavani A, Bosetti C, Boffetta P, La Vecchia C. Coffee and the risk of hepatocellular carcinoma and chronic liver disease: a systematic review and meta-analysis of prospective studies. Eur J Canc Prev 2016;26(5):368−77.

[10] Liu J, Shen B, Shi M, Cai J. Higher caffeinated coffee intake is associated with reduced malignant melanoma risk: a meta-analysis study. PloS One 2016;11:e0147056.

[11] Croft KD. The chemistry and biological effects of flavonoids and phenolic acids. Ann N Y Acad Sci 1998;854:435−42.

[12] Scalbert A, Williamson G. Dietary intake and bioavailability of polyphenols. J Nutr 2000;130. 2073S-85S.

[13] Franke H, Galla HJ, Beuckmann CT. An improved low-permeability in vitro-model of the blood-brain barrier: transport studies on retinoids, sucrose, haloperidol, caffeine and mannitol. Brain Res 1999;818:65−71.

[14] Wong AD, Ye M, Levy AF, Rothstein JD, Bergles DE, Searson PC. The blood-brain barrier: an engineering perspective. Front Neuroeng 2013;6:7.

[15] Ohta A, Sitkovsky M. Methylxanthines, inflammation, and cancer: fundamental mechanisms. Handb Exp Pharmacol 2011: 469−81.

[16] Han ME, Kim HJ, Lee YS, Kim DH, Choi JT, Pan CS, et al. Regulation of cerebrospinal fluid production by caffeine consumption. BMC Neurosci 2009;10:110.

[17] Nehlig A, Daval JL, Debry G. Caffeine and the central nervous system: mechanisms of action, biochemical, metabolic and psychostimulant effects. Brain Res Brain Res Rev 1992;17:139−70.

[18] Lunt MJ, Ragab S, Birch AA, Schley D, Jenkinson DF. Comparison of caffeine-induced changes in cerebral blood flow and middle cerebral artery blood velocity shows that caffeine reduces middle cerebral artery diameter. Physiol Meas 2004;25: 467−74.

[19] Schwarzschild MA, Xu K, Oztas E, Petzer JP, Castagnoli K, Castagnoli Jr N, et al. Neuroprotection by caffeine and more specific A2A receptor antagonists in animal models of Parkinson's disease. Neurology 2003;61:S55−61.

[20] Burch JD, Craib KJ, Choi BC, Miller AB, Risch HA, Howe GR. An exploratory case-control study of brain tumors in adults. J Natl Cancer Inst 1987;78:601−9.

[21] Hochberg F, Toniolo P, Cole P, Salcman M. Nonoccupational risk indicators of glioblastoma in adults. J Neuro Oncol 1990;8: 55−60.

[22] Giles GG, McNeil JJ, Donnan G, Webley C, Staples MP, Ireland PD, et al. Dietary factors and the risk of glioma in adults: results of a case-control study in Melbourne, Australia. Int J Canc 1994;59:357−62.

[23] Lee M, Wrensch M, Miike R. Dietary and tobacco risk factors for adult onset glioma in the San Francisco Bay Area (California, USA). Cancer Causes Control 1997;8:13−24.

[24] Blowers L, Preston-Martin S, Mack WJ. Dietary and other lifestyle factors of women with brain gliomas in Los Angeles County (California, USA). Cancer Causes Control 1997;8:5−12.

[25] Efird JT, Friedman GD, Sidney S, Klatsky A, Habel LA, Udaltsova NV, et al. The risk for malignant primary adult-onset glioma in a large, multiethnic, managed-care cohort: cigarette smoking and other lifestyle behaviors. J Neuro Oncol 2004;68: 57−69.

[26] Holick CN, Smith SG, Giovannucci E, Michaud DS. Coffee, tea, caffeine intake, and risk of adult glioma in three prospective cohort studies. Cancer Epidemiol Biomark Prev 2010;19:39−47. a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology.

[27] Michaud DS, Gallo V, Schlehofer B, Tjonneland A, Olsen A, Overvad K, et al. Coffee and tea intake and risk of brain tumors in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study. Am J Clin Nutr 2010;92:1145–50.

[28] Dubrow R, Darefsky AS, Freedman ND, Hollenbeck AR, Sinha R. Coffee, tea, soda, and caffeine intake in relation to risk of adult glioma in the NIH-AARP Diet and Health Study. Cancer Causes Control 2012;23:757–68.

[29] Ogawa T, Sawada N, Iwasaki M, Budhathoki S, Hidaka A, Yamaji T, et al. Coffee and green tea consumption in relation to brain tumor risk in a Japanese population. Int J Canc 2016; 139(12):2714–21.

[30] Kuan AS, Green J, Kitahara CM, Berrington de Gonzalez A, Key T, Reeves G, et al. Diet and risk of glioma: combined analysis of three large prospective studies in the UK and USA. Neuro Oncol 2019;21(7):944–52.

[31] Hashibe M, Galeone C, Buys SS, Gren L, Boffetta P, Zhang ZF, et al. Coffee, tea, caffeine intake, and the risk of cancer in the PLCO cohort. Br J Canc 2015;113:809–16.

[32] Cote DJ, Bever AM, Wilson KM, Smith TR, Smith-Warner SA, Stampfer MJ. A prospective study of tea and coffee intake and risk of glioma. Int J Canc 2019. https://doi.org/10.1002/ijc.32574.

[33] Collins R. What makes UK Biobank special? Lancet 2012;379: 1173–4.

[34] Ganna A, Ingelsson E. 5 year mortality predictors in 498,103 UK Biobank participants: a prospective population-based study. Lancet 2015;386:533–40.

[35] Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health organization classification of tumors of the central nervous system: a summary. Acta Neuropathol 2016;131:803–20.