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Coffee, tea, soda, and caffeine intake in relation to risk of adult glioma in the NIH-AARP Diet and Health Study

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Abstract

Purpose—We utilized the large, prospective NIH-AARP Diet and Health Study to further explore the hypothesis, suggested by two recent prospective cohort studies, that increased intake of coffee, tea, soda, and/or caffeine is associated with reduced adult glioma risk.

Methods—At baseline in 1995–1996, dietary intake, including coffee, tea, and soda, was assessed with a food frequency questionnaire. We used Cox proportional hazards models to calculate adjusted hazard ratios (HR) and 95 percent confidence intervals (CI) for glioma risk in relation to beverage intake.

Results—During follow-up of 545,771 participants through 2006, 904 participants were diagnosed with glioma. We found no trends of decreasing glioma risk with increasing intake of specific beverages or total caffeine. HR patterns for consumption of the caffeinated versus decaffeinated form of each beverage were inconsistent with a specific caffeine effect. HR patterns of reduced glioma risk for most categories of beverage intake greater than "none" prompted a *post hoc* analysis that revealed borderline-significant inverse associations for any versus no intake of tea (HR = 0.84; 95% CI, 0.69–1.03), total coffee plus tea (HR = 0.70; 95% CI, 0.48–1.03), and soda (HR = 0.82; 95% CI, 0.67–1.01).

Conclusions—The borderline-significant inverse associations could be explained by a threshold effect in which any beverage intake above a low level confers a beneficial effect, most likely due to beverage constituents other than caffeine. They also could be explained by non-drinkers of these beverages sharing unknown extraneous characteristics associated with increased glioma risk, or by chance.

Keywords

glioma; brain neoplasms; coffee; tea; soda; caffeine

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Conflict of interest
The authors declare that they have no conflict of interest.

Introduction

The only known modifiable risk factor for glioma, the most common form of brain cancer, is exposure to high dose ionizing radiation, which accounts for a small proportion of glioma cases [1]. However, two recent prospective cohort studies provided suggestive evidence that coffee, tea, and/or caffeine consumption may be associated with reduced adult glioma risk [2, 3]. These associations are biologically plausible because coffee and tea contain compounds with anticarcinogenic properties, including polyphenols and other antioxidants, and diterpenes and caffeic acid specifically in coffee [4–6]. Laboratory studies of the effects of caffeine, found in coffee, tea, and soda, on cell proliferation and apoptosis have been inconsistent [7]. With respect to glioma in particular, it is well known that caffeine crosses the blood-brain barrier and acts as a central nervous system stimulant. A recent laboratory investigation found that caffeine inhibited migration of glioblastoma (the most common and most lethal form of glioma) cells through mouse brain slices in culture and increased survival in a mouse xenograft model [8].

One of the prospective cohort studies, by Holick et al., which pooled results from Nurses' Health Study I and II and the Health Professionals Follow-up Study and included 335 incident glioma cases, found significant inverse associations between glioma risk and both total coffee plus tea intake and caffeine intake [2]. The latter association was only observed among men. Intakes of coffee, caffeinated coffee, decaffeinated coffee, tea, caffeinated carbonated beverages, and decaffeinated carbonated beverages were unrelated to glioma risk.

The second prospective study, by Michaud et al. and based in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, included 343 incident glioma cases [3]. Using country-specific quantiles of intake, this study found no association between intake of total coffee plus tea, coffee, or tea, and glioma risk. However, the study did observe a significant inverse association between glioma risk and total coffee plus tea intake ≥100 ml/day versus <100 ml/day, suggesting a threshold effect. This study did not examine caffeine intake.

Because results of the two recent prospective cohort studies were suggestive, but not definitive, we utilized the large, prospective NIH-AARP Diet and Health Study cohort to further explore the hypothesis that increased intake of coffee, tea, soda, and/or caffeine is associated with reduced adult glioma risk.

Methods

Study population and cohort follow-up

The NIH-AARP Diet and Health Study, described previously [9], was initiated in 1995–1996 with the mailing of a self-administered questionnaire on demographic characteristics, dietary intake, and health-related behaviors to 3.5 million members of AARP (formerly the American Association of Retired Persons) aged 50 to 71 years who resided in one of six U.S. states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) or two U.S. metropolitan areas (Atlanta, Georgia and Detroit, Michigan). The study was approved by the Special Studies Institutional Review Board of the National Cancer Institute; all subjects provided informed consent on entry.

Of 566,401 participants who satisfactorily completed the questionnaire, we excluded individuals who had questionnaires completed by proxy respondents (n = 15,760) or had prevalent brain cancer at baseline (n = 21). After these exclusions, we further excluded persons who reported extreme values for energy intake, defined as more than two

interquartile ranges above the 75th percentile or below the 25th percentile of Box–Cox log-transformed intake (n = 4,849). The final analytical cohort consisted of 545,771 participants (322,348 men and 223,423 women).

Cohort follow-up methods for vital status and cancer diagnoses have been described previously [10, 11]; follow-up was last updated through December 31, 2006. Cancer diagnoses, including glioma, were identified through probabilistic linkage with state cancer registries. We defined gliomas as malignant brain neoplasms (International Classification of Diseases for Oncology, third edition [ICD-O-3] topography codes C71.0–C71.9 and behavior code 3) with an ICD-O-3 morphology code between 9380 and 9460.

Assessment of coffee, tea, soda, and caffeine intake

At baseline, dietary intake, including coffee, tea, and soda, was assessed with a self-administered 124-item food frequency questionnaire. Participants were asked to report their usual intake over the past year of coffee; hot tea; iced tea; and soft drinks, soda, or pop, diet or regular (henceforth called “soda”), using 10 predefined frequency categories ranging from “never” to “6+ cups per day” for coffee and tea and from “never” to “6+ times per day” for soda. For soda, participants were also queried about portion size.

Participants were then asked “When you drank the following beverages, please mark whether you usually drank caffeine-free or caffeine-containing types.” For each beverage (coffee, hot tea, iced tea, and soda), the choices were “Didn’t drink this beverage,” “More than half the time I drank caffeine-free,” and “More than half the time I drank caffeine-containing.” For the purpose of estimating daily total caffeine intake (mg/day), we assumed that “usually” meant “always.” For each participant, we then summed the product of the estimated caffeine content of each beverage by the daily amount consumed. We also included other caffeine-containing beverages and foods in this calculation. However, 99.4% of total caffeine intake was from coffee, tea, and soda (84.8% from coffee, 9.6% from tea, and 5.0% from soda).

We lacked assessment of type of tea, such as green, black, or herbal, and of type of coffee according to brewing method, such as espresso, boiled, or filtered coffee. Different types of tea and coffee can vary according to the content of caffeine [12, 13] and other pertinent compounds such as polyphenols and diterpenes [5, 14–16]. In a subset of 1,953 cohort participants who completed two nonconsecutive 24-hour dietary recalls, 80% drank ground coffee, 18% instant coffee, and 1% espresso coffee.

Statistical analysis

Hazard ratios (HR) and two-sided 95 percent confidence intervals (CI) for glioma risk in relation to intake of coffee, tea, total coffee plus tea, soda, or total caffeine were estimated using Cox proportional hazards models using the PROC PHREG procedure (SAS version 9.2, SAS Institute, Cary, NC). Follow-up time for each participant extended from the date of return of the baseline questionnaire in 1995–1996 to the date of first brain cancer diagnosis, date of death, date moved out of a cancer registry ascertainment area, or date of last follow-up on December 31, 2006, whichever occurred first. Follow-up time was used as the underlying time metric. For all comparisons, p-values were based upon 2-sided tests with $p < 0.05$ indicating statistical significance.

We classified intake of coffee, tea (hot plus iced), total coffee plus tea, and soda into pre-specified categories, ranging from none to ≥6 cups/day for coffee; none to >3 cups/day for tea; none to >5 cups/day for total coffee plus tea; and none to >2 cans/day for soda. In addition, for each beverage we included a “missing” category for those missing information about the quantity of intake.

We also classified intake of coffee, tea (hot plus iced), and soda into pre-specified categories with respect to caffeine content. For each beverage, we characterized each participant as a non-drinker of the beverage; a drinker of the beverage with caffeine more than half the time; a drinker of the beverage caffeine-free more than half the time; a drinker of the beverage, but with missing information about caffeine intake; or having missing information about quantity of intake of the beverage. For the analysis of tea, if a participant drank both hot tea and iced tea, but drank one caffeine-containing more than half the time and the other caffeine-free more than half the time, we considered the participant to be a tea drinker with missing information about caffeine intake. We did not attempt to classify total coffee plus tea intake according to caffeine content due to inability to classify about one-third of the participants as a result of missing information about caffeine intake of coffee or tea, missing information about the quantity of intake of coffee or tea, or discrepant reporting for a given participant about usual caffeine content of coffee versus tea (i.e.., a participant who drank both coffee and tea, but drank one caffeine-containing more than half the time and the other caffeine-free more than half the time). Finally, we classified total caffeine intake into quintiles.

In “base” multivariate models, we adjusted for age (continuous), sex, and race/ethnicity (non-Hispanic White, non-Hispanic Black, and other). In “full” multivariate models, in addition to these variables we also adjusted for energy intake (continuous; kcal per day), height (<1.60, 1.60 to 1.64, 1.65 to 1.69, 1.70 to 1.74, 1.75 to 1.79, 1.80 to 1.84, 1.85 to 1.89, ≥1.90 meters, and missing), fruit and vegetable intake (quintiles; cups per 1,000 kcal per day), and nitrite intake from plant sources (quintiles; mg per 1,000 kcal per day). We adjusted for the latter three variables because they have been shown to be associated with glioma in this cohort [17, 18]. We included energy intake because the latter two variables were adjusted for energy intake using the nutrient density method [19].

For intake of coffee, tea, or soda, we conducted tests for linear trend by assigning participants their quantity of intake and modeling this value as a continuous variable, with the *p*-value determined by a Wald test. For intake of total caffeine, we assigned participants the median intake for their category and modeled this median value as a continuous variable. To test for sex heterogeneity in the relationship between intake of a beverage or total caffeine and glioma risk, we added a cross-product term between intake of the beverage or total caffeine and sex to the multivariate model, with $p_{heterogeneity}$ determined by a Wald test for the cross-product term. Because no $p_{heterogeneity}$ for sex was statistically significant, we do not present sex-specific results, with the exception of results for total caffeine intake. In selected analyses we mutually adjusted beverage intake variables for each other. We tested the proportional hazards assumption by examining correlations between the natural logarithm of person-years and Schoenfeld residuals for intake of each beverage or total caffeine in full multivariate models. Consistent with proportional hazards, we observed no p-values < 0.05 for these correlations.

To test the robustness of our findings, we conducted several alternative analyses. First, we excluded 50,801 participants (9.3%) with a history of cancer at baseline. Second, to account for the possible influence of pre-mortal disease or preclinical manifestations of glioma on baseline beverage intake, we excluded the first two years of follow-up, dropping 16,704 participants (3.1%) with follow-up less than two years. Third, we restricted the outcome to microscopically-confirmed glioma. Because the Pennsylvania Cancer Registry did not provide data on microscopic confirmation, for these analyses we excluded 81,813 participants (15.0%) with a baseline residence or a glioma diagnosed in Pennsylvania and compared results for all versus microscopically-confirmed gliomas as the outcome with these participants excluded.

Results

The median age at baseline of cohort participants was 62.8 years. The cohort was well-educated (38.6% college graduate/postgraduate) and predominantly non-Hispanic White (91.4%). During 5,268,995 person-years of follow-up (median follow-up 10.6 years), 904 cases of glioma (635 among men and 269 among women) were identified.

Table 1 shows baseline characteristics of study participants by coffee, tea, and soda intake. At baseline, high coffee intake was associated with male sex, non-Hispanic White race/ethnicity, higher energy intake, lower fruit and vegetable intake, and lower intake of nitrite from plant sources. High tea intake was associated with female sex, non-Hispanic White race/ethnicity, and higher energy intake. High soda intake was associated with younger age, male sex, higher energy intake, taller height, lower fruit and vegetable intake, and lower intake of nitrite from plant sources.

In Table 2 we tested the hypotheses that increased intake of coffee, tea, total coffee plus tea, or soda is associated with reduced glioma risk. We observed no significant trends of decreasing glioma risk with increasing beverage intake. However, in the base multivariate model, there was a significant inverse association between the highest level of tea intake (>3 cups per day) and glioma risk (HR = 0.75; 95% CI, 0.57–0.99) that remained borderline-significant in the full multivariate model (HR = 0.75; 95% CI, 0.57–1.00). Furthermore, in the base multivariate model there also was a significant inverse association between the highest level of total coffee plus tea intake (>5 cups/day) and glioma risk (HR = 0.65; 95% CI, 0.43–0.97) that remained borderline-significant in the full multivariate model ((HR = 0.68; 95% CI, 0.46–1.03). Results did not meaningfully differ after mutual adjustment for coffee, tea, and soda intake or for mutual adjustment of total coffee plus tea and soda intake.

In Table 3 we modeled intake of caffeinated and decaffeinated coffee, tea, and soda in relation to glioma risk in order to test the hypothesis that increased consumption of specific caffeinated beverages is associated with reduced glioma risk. We observed no significant HRs for the highest versus lowest levels of caffeinated or decaffeinated beverage intake and no significant trends of decreasing glioma risk with increasing caffeinated or decaffeinated beverage intake. Results did not meaningfully differ after mutual adjustment for coffee, tea, and soda intake categorized according to caffeinated/decaffeinated content as in Table 3.

In Table 4 we tested the hypothesis that increased total caffeine intake is associated with reduced glioma risk. Although the $p_{\text{heterogeneity}}$ for sex for total caffeine intake was 0.69 in the full multivariate model, because Holick et al. reported a significant inverse association between total caffeine intake and glioma risk among men, but not among women [2], we also present sex-specific HRs in Table 4. We observed no significant HRs for the highest versus lowest quintiles and no significant trends of decreasing glioma risk with increasing intake for all participants or for men or women separately.

The HR patterns in Table 2 of reduced glioma risk for most categories of intake greater than "None" suggested an inverse association between glioma risk and any versus no intake, consistent with Michaud et al's observation of a threshold effect for total coffee plus tea intake at a relatively low level of intake. We therefore conducted a *post hoc* analysis in which we calculated HRs for any versus no intake, observing borderline-significant associations between glioma risk and any vs. no intake of tea (full multivariate-adjusted HR = 0.84; 95% CI, 0.69–1.03), total coffee plus tea (full multivariate-adjusted HR = 0.70; 95% CI, 0.48–1.03), and soda (full multivariate-adjusted HR = 0.82; 95% CI, 0.67–1.01) (Table 5). For any versus no intake of coffee, tea, or soda, respectively, the inverse association did not tend to be stronger for the caffeinated than for the decaffeinated form of the beverage (Table 5). Finally, we dichotomized total coffee plus tea intake as >0.5 cups/day versus ≤0.5

cups/day. The base multivariate-adjusted HR for >0.5 cups/day was 0.80 (95% CI, 0.64–1.00) and the full multivariate-adjusted HR was 0.82 (95% CI, 0.66–1.03) (data not shown in table).

We conducted three sets of alternative analyses in which we excluded participants with a history of cancer at baseline, excluded the first two years of follow-up, and restricted the outcome to microscopically-confirmed glioma (after excluding participants with a baseline residence or a glioma diagnosed in Pennsylvania because the Pennsylvania Cancer Registry did not provide data on microscopic confirmation). The results of these alternative analyses (not shown) did not meaningfully differ from the results of the primary analyses, with the exception of the results for tea intake with the outcome restricted to microscopically-confirmed cases. These results were essentially null and were driven in part by the exclusion from these analyses of participants with a baseline residence or a glioma diagnosed in Pennsylvania and in part by the exclusion of microscopically-confirmed cases per se.

Discussion

Our results provided little support for an inverse association between caffeine intake and glioma risk. We found no evidence of a dose-response relationship for total caffeine intake (Table 4) or for intake of specific caffeinated beverages (Table 3). Furthermore, the HR pattern for consumption of the caffeinated versus decaffeinated form of each beverage was inconsistent with a specific caffeine effect (Tables 3 and 5). In the pooled results from Nurses' Health Study I and II and the Health Professionals Follow-up Study, Holick et al. observed a significant inverse association between caffeine intake and glioma risk among men, but not women [2]. They did not report a sex-adjusted overall result or whether there was significant sex heterogeneity. In the current study, for total caffeine intake $p_{\text{heterogeneity}}$ for sex was 0.69, indicating no sex heterogeneity. In the EPIC study, Michaud et al. did not evaluate total caffeine consumption, but reported no association between caffeinated coffee intake and glioma risk [3]. Thus, the weight of the evidence from these 3 cohort studies suggests that caffeine intake is unrelated to glioma risk.

Although we observed no evidence for a dose-response relationship between intake of coffee, tea, total coffee plus tea, or soda and glioma risk (Table 2), we did observe borderline-significant inverse associations between glioma risk and the highest levels of intake of tea and of total coffee plus tea. Furthermore, our post hoc analysis showed borderline-significant inverse associations between glioma risk and any versus no intake of tea, total coffee plus tea, or soda, respectively (Table 5). These "any versus no intake" inverse associations could be explained by a threshold effect in which any beverage intake above a low level was sufficient to confer a complete beneficial effect, by non-drinkers of these beverages sharing unknown extraneous characteristics associated with increased glioma risk, or by chance.

In the Nurses' Health Study/Health Professionals Follow-up Study cohort, Holick et al. observed a HR of 0.60 (95% CI, 0.41–0.87) for the highest (≥5 cups/day) versus lowest (0 to 1 cup/day) level of total coffee plus tea intake ($p_{\text{trend}} = 0.04$), but observed no significant HRs or trends for coffee, tea, or soda consumption individually [2]. In the EPIC study, Michaud et al. observed no association between tea or herbal tea intake and glioma risk and observed no significant HRs or trends for total coffee plus tea intake when categorized according to quintiles. However, they reported a significant threshold effect for ≥100 ml/day versus <100 ml/day of total coffee plus tea intake (HR = 0.66; 95% CI, 0.44–0.97) [3]. Because tea and coffee consumption patterns, including coffee brewing method that affects the chemical content of coffee, vary substantially across geographic regions [3], 100 ml of total coffee plus tea in the EPIC study is not necessarily equivalent to 100 ml of total coffee

plus tea in the current study. Nevertheless, 100 ml in volume is equivalent to about 0.4 U.S. cups in volume. We observed a borderline-significant threshold effect for >0.5 cups/day versus ≤0.5 cups/day of total coffee plus tea intake.

If there is, in fact, an inverse association between tea, total coffee plus tea, or soda intake and glioma risk, it is most likely due to beverage constituents other than caffeine. Neither the Holick et al. study, the Michaud et al. study, nor our study took into account type of tea consumed (i.e., green versus black) or coffee brewing method. Anti-glioma effects could vary between black and green tea (e.g., certain catechins found in abundance specifically in green tea were reported to have anti-glioma properties *in vitro* [14]). Furthermore, coffee brewing method influences the chemical content of coffee (e.g., the diterpene content of filtered coffee is negligible compared to that of boiled or French press coffee [16]). In a recent population-based cohort study in Northern Sweden, some heterogeneity in risk of specific cancer types was observed according to consumption of filtered versus boiled coffee [20]. We suggest that further research is needed that takes into account type of tea consumed and coffee brewing method. We do not have a hypothesis about a non-caffeine constituent of soda that could protect against glioma risk.

Results from six other epidemiologic studies, apart from the current study, the Holick et al. study, and the Michaud et al. study, were inconsistent. In the only other cohort study, based in the Kaiser Permanente Medical Care Program of Northern California (130 incident glioma cases), coffee consumption was associated with elevated glioma risk (HR for ≥7 versus <1 cup/day = 1.7; 95% CI, 0.8–3.6; p_{trend} = 0.05) [21]. However, in two case-control studies, no association was observed between glioma risk and coffee [22, 23] or tea [22] intake. In another case-control study of women in Los Angeles County, USA, consumption of total coffee, tea, plus cola was inversely associated with glioma risk (odds ratio for highest versus lowest quartile = 0.3; 95% CI, 0.1–1.2; p_{trend} = 0.03) [24], and in a case-control study in Melbourne, Australia, intake of “caffeine drinks” (no further elaboration) was inversely associated with glioma risk in women, but not in men [25]. In contrast, in a case-control study in the San Francisco Bay Area, California, USA, no association was observed between consumption of “other drinks,” which included coffee, tea, and soda, and glioma risk [26]. Finally, in case-control studies, intake of “soft drinks” [22] and “cola drinks” [25] were not associated with glioma risk.

Our study had several limitations. First, beverage intake was measured via a food frequency questionnaire, which is subject to measurement error [27]. Second, assessment of intake of caffeinated and decaffeinated beverages was imprecise, which could have led to misclassification of intake of the caffeinated and decaffeinated forms of coffee, tea, and soda, as well as of total caffeine intake. Third, because the questionnaire assessed beverage intake at a single point in time (usual intake during the year before baseline), we may not have measured intake during the etiologically relevant exposure period. Fourth, our choice to use “pure” reference groups of non-drinkers of coffee, tea, or soda led to an advantageous homogeneity of exposure within the reference group but a relative loss of precision in HR estimates due to a lower number of participants relative to a non-“pure” reference group that would include both non-drinkers and low-frequency beverage consumers. Finally, as mentioned above, although anti-glioma effects could vary by type of tea and by coffee brewing method, we did not collect information about these variables.

This study also had strengths. It was the largest prospective cohort study to test the hypothesis that coffee, tea, soda, and/or caffeine intake is associated with reduced adult glioma risk, with more than twice the number of incident cases than the other two prospective cohort studies (904 incident cases compared with 335 incident cases in the Holick et al. study and 343 incident cases in the Michaud et al. study). The prospective

design had advantages over previous case-control studies by protecting against recall and selection bias as well as against use of proxy respondents (common in glioma case-control studies). In addition, there was a wide range of beverage intake and we were able to control for potential confounders. Finally, the general consistency of alternative analyses with our primary analyses showed our results to be robust.

In conclusion, our results provided little support for an inverse association between caffeine intake and glioma risk. Although we observed no dose-response relationships, we observed borderline-significant inverse associations between glioma risk and the highest levels of intake of tea and of total coffee plus tea as well as any versus no consumption of tea, total coffee plus tea, and soda, respectively. The latter associations could be explained by a threshold effect in which any beverage intake above a low level conferred a beneficial effect, by non-drinkers of these beverages sharing unknown extraneous characteristics associated with increased glioma risk, or by chance. Any true association between beverage intake and glioma risk is most likely due to beverage constituents other than caffeine. Because the concentration of these constituents in tea or coffee is related to the type of tea and the type of coffee brewing method, these variables should be carefully measured and taken into account in future studies.

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Table 1

Baseline characteristics of study participants by coffee, tea and soda intake in the NIH-AARP Diet and Health Study

Beverage Characteristic	**Quantity of intake**					
Coffee (cups/day):	None	<1	1	2 to 3	4 to 5	>6
Participants	55,538	89,881	90,370	222,209	65,089	19,919
Age[a] (years)	61.8	62.7	63.9	63.0	61.8	61.1
Male (%)	51.5	56.1	54.9	61.0	66.4	67.6
Non-Hispanic White (%)	90.5	87.5	89.7	94.9	96.9	97.3
Energy intake[a] (kcal/day)	1,638	1,599	1,624	1,698	1,829	1,989
Height[a] (meters)	1.70	1.73	1.70	1.73	1.75	1.75
Fruit and vegetable intake[a,b]	2.4	2.4	2.3	2.1	1.9	1.7
Nitrite intake from plant sources[a,c]	0.43	0.44	0.43	0.41	0.39	0.37
Tea (cups/day):	None	>0 to ≤0.5	>0.5 to ≤1	>1 to ≤2	>2 to ≤3	>3
Participants	54,480	186,191	97,439	56,750	79,150	65,431
Age[a] (years)	63.6	62.9	62.7	62.9	62.5	62.3
Male (%)	65.7	61.2	60.3	52.1	59.3	51.7
Non-Hispanic White (%)	91.5	91.4	92.6	93.0	94.9	94.6
Energy intake[a] (kcal/day)	1,679	1,616	1,678	1,680	1,757	1,859
Height[a] (meters)	1.73	1.73	1.73	1.70	1.73	1.70
Fruit and vegetable intake[a,b]	2.1	2.2	2.2	2.3	2.1	2.2
Nitrite intake from plant sources[a,c]	0.40	0.42	0.42	0.44	0.41	0.42
Soda (cans/day):	None	>0 to ≤0.1	>0.1 to ≤0.5	>0.5 to ≤1	>1 to ≤2	> 2
Participants	53,336	150,351	130,923	71,767	63,186	65,369
Age[a] (years)	64.5	63.7	63.1	62.2	61.3	60.2
Male (%)	46.0	53.9	60.4	68.2	61.7	66.5
Non-Hispanic White (%)	93.4	92.5	92.3	91.6	93.3	93.9
Energy intake[a] (kcal/day)	1,573	1,580	1,646	1,797	1,811	1,958
Height[a] (meters)	1.70	1.70	1.73	1.75	1.73	1.75

Beverage Characteristic	Quantity of intake					
Fruit and vegetable intake[a,b]	2.6	2.3	2.2	2.0	2.0	1.9
Nitrite intake from plant sources[a,c]	0.47	0.43	0.42	0.39	0.39	0.37

[a] Median value

[b] MyPeriod Equivalents Database (MPED) cup equivalents/1,000 kcal per day

[c] mg/1,000 kcal per day

Table 2

Multivariate-adjusted hazard ratios and 95% confidence intervals according to category of coffee, tea and soda intake and glioma risk

Beverage	**Quantity of intake[a]**						P_{trend}
Coffee (cups/day):	None	>0 to <1	1	2 to 3	4 to 5	≥6	
Number of cases	93	127	151	409	87	34	
Number of participants	55,538	89,881	90,370	222,209	65,089	19,919	
Base multivariate HR[b]	1.00	0.83	0.96	1.02	0.73	0.95	.60
95% CI	(ref)	0.63–1.08	0.74–1.24	0.81–1.27	0.55–0.98	0.64–1.41	
Full multivariate HR[c]	1.00	0.82	0.96	1.04	0.77	1.04	.91
95% CI	(ref)	0.62–1.07	0.74–1.24	0.83–1.30	0.57–1.03	0.70–1.55	
Tea (cups/day):	None	>0 to ≤0.5	>0.5 to ≤1	>1 to ≤2	>2 to ≤3	>3	
Number of cases	106	298	169	88	147	91	
Number of participants	54,480	186,191	97,439	56,750	79,150	65,431	
Base multivariate HR[b]	1.00	0.83	0.90	0.82	0.96	0.75	.24
95% CI	(ref)	0.66–1.03	0.70–1.15	0.62–1.09	0.75–1.23	0.57–0.99	
Full multivariate HR[c]	1.00	0.81	0.88	0.80	0.96	0.75	.35
95% CI	(ref)	0.65–1.02	0.69–1.12	0.60–1.06	0.74–1.23	0.57–1.00	
Total coffee plus tea (cups/day):	None	>0 to ≤1	>1 to ≤2	>2 to ≤3	>3 to ≤5	>5	
Number of cases	27	105	109	213	265	177	
Number of participants	11,622	67,154	73,728	127,998	143,443	113,832	
Base multivariate HR[b]	1.00	0.68	0.63	0.68	0.76	0.65	.22
95% CI	(ref)	0.44–1.04	0.41–0.96	0.46–1.02	0.51–1.13	0.43–0.97	
Full multivariate HR[c]	1.00	0.67	0.63	.70	0.78	0.68	.55
95% CI	(ref)	0.44–1.03	0.41–0.95	0.47–1.04	0.52–1.16	0.46–1.03	
Soda (cans/day):	None	>0 to ≤0.1	>0.1 to ≤0.5	>0.5 to ≤1	>1 to ≤2	> 2	
Number of cases	102	249	213	121	92	105	
Number of participants	53,336	150,351	130,923	71,767	63,186	65,369	
Base multivariate HR[b]	1.00	0.83	0.80	0.81	0.73	0.80	.92

Beverage	Quantity of intake[a]						P_{trend}
95% CI	(ref)	0.66–1.05	0.63–1.01	0.62–1.06	0.55–0.96	0.61–1.06	
Full multivariate HR[c]	1.00	0.84	0.80	0.84	0.76	0.87	.53
95% CI	(ref)	0.66–1.05	0.63–1.02	0.65–1.10	0.57–1.01	0.65–1.15	

Abbreviations: HR, hazard ratio; CI, confidence interval

[a]Multivariate models included a category for those missing information on the quantity of beverage intake; the number of missing values for coffee was 2,765 (0.5%); for tea, 6,330 (1.2%); for total coffee plus tea, 7,994 (1.5%); and for soda, 10,839 (2.0%).

[b]Adjusted for age, sex and race/ethnicity

[c]Adjusted for age, sex, race/ethnicity, energy intake, height, fruit and vegetable intake, and nitrite intake from plant sources

Table 3

Multivariate-adjusted hazard ratios and 95% confidence intervals according to category of caffeinated and decaffeinated intake of coffee, tea, and soda and glioma risk

Beverage	**Quantity of caffeinated/decaffeinated intake**										
	Non-drinker	**Drank caffeinated beverage more than ½ time**					**Drank decaffeinated beverage more than ½ time**				
Coffee (cups/day):	None	>0 to <1	1	2 to 3	4 to 5	≥6	>0 to <1	1	2 to 3	4 to 5	≥6
Cases	93	51	83	290	67	25	65	64	105	18	8
Participants	55,538	37,022	52,407	152,291	48,473	15,642	45,515	34,865	62,955	14,549	3,649
Base multivariate HR[b]	1.00	0.80	0.91	1.05	0.76	0.90	0.84	1.04	0.91	0.67	1.21
95% CI	(ref)	0.57–1.12	0.67–1.22	0.83–1.33	0.55–1.04	0.58–1.39	0.61–1.15	0.76–1.44	0.69–1.21	0.40–1.10	0.59–2.49
P_{trend}						.54					.63
Full multivariate HR[c]	1.00	0.81	0.92	1.08	0.81	0.99	0.81	1.03	0.91	0.67	1.26
95% CI	(ref)	0.57–1.13	0.68–1.24	0.86–1.37	0.59–1.11	0.63–1.54	0.59–1.12	0.75–1.42	0.69–1.20	0.41–1.12	0.61–2.60
P_{trend}						.96					.75
Tea (cups/day):	None	>0 to ≤0.5	>0.5 to ≤1	>1 to ≤2	>2 to ≤3	>3	>0 to ≤0.5	>0.5 to ≤1	>1 to ≤2	>2 to ≤3	>3
Cases	106	189	110	46	85	60	51	30	20	38	18
Participants	54,480	116,078	60,810	32,388	49,592	39,457	33,165	19,476	11,675	17,013	15,159
Base multivariate HR[b]	1.00	0.83	0.92	0.74	0.88	0.81	0.83	0.84	0.95	1.18	0.66
95% CI	(ref)	0.65–1.05	0.70–1.20	0.52–1.04	0.66–1.16	0.59–1.11	0.60–1.16	0.56–1.25	0.59–1.54	0.82–1.71	0.40–1.09
P_{trend}						.43					.28
Full multivariate HR[c]	1.00	0.83	0.91	0.73	0.88	0.82	0.79	0.79	0.90	1.14	0.64
95% CI	(ref)	0.65–1.05	0.70–1.19	0.51–1.03	0.66–1.18	0.60–1.13	0.56–1.10	0.53–1.19	0.56–1.45	0.79–1.65	0.39–1.06
P_{trend}						.56					.26
Soda (cans/day):	None	>0 to ≤0.1	>0.1 to ≤0.5	>0.5 to ≤1	>1 to ≤2	> 2	>0 to ≤0.1	>0.1 to ≤0.5	>0.5 to ≤1	>1 to ≤2	>2
Cases	102	123	119	72	48	56	92	87	43	43	49
Participants	53,336	72,057	62,149	41,093	33,296	32,240	55,234	61,938	27,012	26,872	30,162
Base multivariate HR[b]	1.00	0.84	0.94	0.84	0.72	0.88	0.86	0.69	0.78	0.80	0.81
95% CI	(ref)	0.65–1.10	0.72–1.22	0.62–1.13	0.51–1.02	0.64–1.23	0.65–1.14	0.52–0.92	0.55–1.12	0.56–1.15	0.57–1.14

Beverage	Quantity of caffeinated/decaffeinated intake										
	Non-drinker	Drank caffeinated beverage more than ½ time					Drank decaffeinated beverage more than ½ time				
P_{trend}						.70					.65
Full multivariate HR[c]	1.00	0.87	0.97	0.90	0.78	1.00	0.84	0.68	0.79	0.81	0.85
95% CI	(ref)	0.67–1.13	0.74–1.26	0.66–1.22	0.55–1.10	0.71–1.40	0.63–1.11	0.51–0.91	0.55–1.13	0.57–1.17	0.60–1.19
P_{trend}						.24					.94

Abbreviations: HR, hazard ratio; CI, confidence interval

[a]Multivariate models included categories for participants with a missing value for quantity of beverage intake and for drinkers of the beverage with a missing value for caffeinated vs. decaffeinated intake; the total number missing for coffee was 22,865 (4.2%); for tea, 96,478 (17.7%); and for soda, 50,382 (9.2%).

[b]Adjusted for age, sex and race

[c]Adjusted for age, sex, race, energy intake, height, fruit and vegetable intake, and nitrite intake from plant sources

Table 4

Multivariate hazard ratios (HR) and 95% confidence intervals (CI) according to quintile of total caffeine intake and glioma risk

	Quintile of intake[a]					
Total caffeine intake	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	P_{trend}
Median intake (mg/day):	8	47	238	541	948	
All study participants						
Number of cases	176	140	140	200	152	
Number of participants	96,867	96,861	96,868	96,854	96,868	
Base multivariate HR[b]	1.00	0.77	0.81	1.07	0.82	.99
95% CI	(ref)	0.62–0.96	0.64–1.01	0.87–1.31	0.66–1.02	
Full multivariate HR[c]	1.00	0.80	0.85	1.12	0.90	.41
95% CI	(ref)	0.64–1.00	0.68–1.06	0.91–1.38	0.72–1.13	
Men						
Number of cases	108	106	89	149	113	
Number of participants	50,540	57,574	49,506	61,986	65,283	
Base multivariate HR[b]	1.00	0.86	0.85	1.12	0.83	.76
95% CI	(ref)	0.66–1.13	0.64–1.13	0.87–1.43	0.64–1.08	
Full multivariate HR[c]	1.00	0.91	0.92	1.20	0.94	.58
95% CI	(ref)	0.69–1.19	0.69–1.21	0.94–1.55	0.71–1.23	
Women						
Number of cases	68	34	51	51	39	
Number of participants	46,327	39,287	47,362	34.868	31,585	
Base multivariate HR[b]	1.00	0.59	0.73	0.98	0.85	.57
95% CI	(ref)	0.39–0.89	0.51–1.05	0.68–1.41	0.57–1.26	
Full multivariate HR[c]	1.00	0.60	0.74	1.00	0.87	.47
95% CI	(ref)	0.39–0.90	0.51–1.07	0.69–1.44	0.58–1.30	

Abbreviations: HR, hazard ratio; CI, confidence interval

[a]Multivariate models included a category for the 61,453 (11%) participants with a missing value for quantity of coffee or tea intake or for caffeinated vs. decaffeinated intake of coffee or tea.

[b]Adjusted for age, sex and race

[c] Adjusted for age, sex, race, energy intake, height, fruit and vegetable intake, and nitrite intake from plant sources

Table 5

Multivariate-adjusted hazard ratios and 95% confidence intervals according to intake of any versus none for coffee, tea, soda, total coffee plus tea, and caffeinated and decaffeinated coffee, tea, and soda, and glioma risk

Beverage	Quantity of intake			
		Any (> 0)		
	None	Drinker of beverage (caffeinated or decaffeinated)[a]	Drinker of beverage[b]	
			Caffeinated more than ½ time	Decaffeinated more than ½ time
Coffee				
Number of cases	93	808	516	260
Number of participants	55,538	487,468	305,835	161,533
Base multivariate HR[c]	1.00	0.93	0.94	0.90
95% CI	(ref)	0.75–1.15	0.76–1.18	0.71–1.14
Full multivariate HR[d]	1.00	0.94	0.97	0.89
95% CI	(ref)	0.76–1.17	0.78–1.22	0.70–1.13
Tea				
Number of cases	106	793	490	157
Number of participants	54,480	484,961	298,325	96,488
Base multivariate HR[c]	1.00	0.85	0.84	0.88
95% CI	(ref)	0.70–1.05	0.68–1.04	0.69–1.13
Full multivariate HR[d]	1.00	0.84	0.84	0.84
95% CI	(ref)	0.69–1.03	0.68–1.04	0.66–1.08
Soda				
Number of cases	102	780	418	314
Number of participants	53,336	481,596	240,835	201,218
Base multivariate HR[c]	1.00	0.80	0.86	0.78
95% CI	(ref)	0.65–0.99	0.69–1.07	0.62–0.98
Full multivariate HR[d]	1.00	0.82	0.90	0.78
95% CI	(ref)	0.67–1.01	0.72–1.13	0.62–0.98
Total coffee plus tea				
Number of cases	27	869		
Number of participants	11,622	526,155		
Base multivariate HR[c]	1.00	0.69		
95% CI	(ref)	0.47–1.01		
Full multivariate HR[d]	1.00	0.70		
95% CI	(ref)	0.48–1.03		

Abbreviations: HR, hazard ratio; CI, confidence interval

[a]Multivariate models included a category for participants with a missing value for quantity of beverage intake; the number of missing values for coffee was 2,765 (0.5%); for tea, 6,330 (1.2%); for total coffee plus tea, 7,994 (1.5%); for soda, 10,839 (2.0%), and for caffeine, 61,453 (11%).

[b] Multivariate models included categories for participants with a missing value for quantity of beverage intake and for drinkers of the beverage with a missing value for caffeinated vs. decaffeinated intake; the total number missing for coffee was 22,865 (4.2%); for tea, 96,478 (17.7%); and for soda, 50,382 (9.2%).

[c] Adjusted for age, sex and race/ethnicity

[d] Adjusted for age, sex, race/ethnicity, energy intake, height, fruit and vegetable intake, and nitrite intake from plant sources