HHS Public Access

Author manuscript

*Eur J Epidemiol*. Author manuscript; available in PMC 2022 September 04.

Published in final edited form as:

*Eur J Epidemiol*. 2021 September ; 36(9): 965–974. doi:10.1007/s10654-021-00800-1.

# Alcohol intake and risk of glioma: results from three prospective cohort studies

**David J. Cote, PhD**[1,2], **Claudine M. Samanic, PhD**[3], **Timothy R. Smith, MD, PhD, MPH**[2], **Molin Wang, PhD**[1,4], **Stephanie A. Smith-Warner, PhD**[4,5], **Meir J. Stampfer, MD, DrPH**[1,4,5], **Kathleen M. Egan, ScD**[6]

[1]Channing Division of Network Medicine, Brigham and Women's Hospital, Boston, MA

[2]Computational Neuroscience Outcomes Center, Department of Neurosurgery, Brigham and Women's Hospital, Boston, MA

[3]Department of Biostatistics and Bioinformatics, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL

[4]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA

[5]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA

[6]Department of Cancer Epidemiology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL

## Abstract

**Purpose:** The association between alcohol intake and glioma remains unclear. We evaluated the association between alcohol intake and incidence of glioma in three large, prospective cohort studies with repeated alcohol assessments.

**Methods:** We harnessed data from three studies with repeat alcohol assessment to compute hazard ratios (HR) and 95% confidence intervals (CI) for glioma by overall alcohol intake and intake from specific beverages using Cox proportional hazards regression, adjusted for age, cohort, body mass index, smoking status, and caloric intake. Analyses were conducted separately for glioma overall and for glioblastoma (GBM).

**Results:** We confirmed 554 incident glioma cases (362 GBM) among 237,505 participants with 6,216,378 person-years of follow up. Cumulative average alcohol intake was associated with reduced risk of glioma (HR=0.75, 95%CI:0.56–0.99 comparing >8–15 to ≤0.5 g/d; HR=0.71, 95%CI:0.53–0.96 comparing >15 g/d to ≤0.5 g/d). When stratified by sex, for the same comparisons, the HRs for men were 0.57 (95%CI:0.36–0.89) and 0.79 (0.53–1.16), and for women 0.90 (95%CI:0.62–1.30) and 0.62, 95%CI:0.39–0.97. Results were consistent when examining cumulative average, baseline, and recent intake, and with a 4 year lag.

**Corresponding author:** David J. Cote, PhD, Department of Epidemiology, Channing Division of Network Medicine, Harvard T.H. Chan School of Public Health, Brigham and Women's Hospital, 181 Longwood Avenue, Boston, MA 02115, Phone: 617.525.2749 Fax: 617.525.2008, david_cote@hms.harvard.edu.

Declarations

Conflicts of Interest

The authors report no conflicts of interest.

**Conclusion:** These results provide evidence against a positive association between alcohol intake and glioma risk. Alcohol intake was associated with reduced risk of glioma in both men and women.

### Keywords

glioma; glioblastoma; cohort; epidemiology; alcohol; beer; wine; liquor

## Introduction

Glioma is the most common primary brain malignancy and the high-grade form, glioblastoma, is associated with a median survival of 15 months with standard treatment [1]. Few modifiable risk factors for these lesions have been identified, but most studies have been limited by a small number of glioma cases or retrospective design [2].

While alcohol has been linked to higher incidence of a variety of cancers, including those of the liver,[3] larynx,[4] colon,[3] esophagus,[4] and breast,[5] results from several studies have shown mixed evidence for an association between alcohol intake and glioma [6–11]. In addition, low to moderate alcohol consumption and heavy alcohol consumption often differ in their association with chronic diseases, such as stroke and cardiovascular disease, which are positively associated with heavy alcohol consumption but inversely associated with low to moderate consumption, compared to never use [12, 13]. Few of the existing studies of alcohol use and glioma have used prospective data [3, 6–8, 11, 14] and none have reported repeat assessments of alcohol intake.

In this study, we used data from three, large, prospective cohort studies—the Nurses' Health Study (NHS), Health Professionals Follow-Up Study (HPFS), and Nurses' Health Study II (NHSII)—to examine the association between alcohol intake and glioma risk. In addition, we examined the associations between intake of alcohol from specific alcoholic beverages, including beer, red and white wine, and liquor, and incidence of glioma.

## Methods

### Study Participants

The methods of the NHS, HPFS, and NHSII have previously been described in detail [15]. In 1976, NHS enrolled 121,701 female nurses aged 30–55 years. In 1986, HPFS enrolled 51,529 male health professionals aged 40–75 years. In 1989, NHSII enrolled 116,686 female nurses aged 25–42 years. Participants in each cohort completed a baseline questionnaire and subsequent biennial follow-up questionnaires. Follow-up rates in the cohorts have exceeded 90% [16]. The Institutional Review Boards at the Brigham and Women's Hospital, Harvard T.H. Chan School of Public Health, and participating registries approved this study.

### Dietary and Alcohol Intake Assessment

Food frequency questionnaires (FFQs) were initially collected in 1980 for 92,468 women in NHS, in 1986 for 49,935 men in HPFS, and in 1991 for 95,391 women in NHSII. For the NHS, a 61-item semi-quantitative FFQ was used at baseline [17]. This was then expanded

to approximately 130 food and beverage items in 1984 and 1986, and repeated every four years subsequently. In HPFS and NHSII, baseline diet was assessed using a 131-item FFQ with updates every four years thereafter [18]. For each item on the FFQ, participants were prompted to report their average intake over the preceding year for a specified serving size of each item. Options ranged from never or almost never to six or more times per day.

Intake of specified portions of beer, wine, and liquor was assessed on each questionnaire, starting from the baseline dietary assessment in each cohort. The portion size was 1 can, bottle, or glass for beer, a 4 oz. glass for wine until 2002/3, at which point it was changed to a 5 oz. glass; and 1 drink or shot for liquor. The 1980 FFQ in the NHS only asked about total wine intake. For that FFQ, total wine intake was divided in half and assigned evenly to red and white wine for inclusion in the analyses of red and white wine. For all other FFQs, red and white wine were asked separately and total wine was computed as the sum of servings of white wine and red wine intake per week. Beginning in 1994 in NHS and HPFS and in 1991 in NHSII, light beer was asked separately from regular beer. For these FFQs, total beer intake was calculated as the sum of reported regular beer and light beer intake. Total alcoholic beverage consumption was calculated as the sum of servings of total beer, total wine, and liquor intake.

Alcohol intake for specific beverages was computed by multiplying the frequency of consumption of that alcoholic beverage by the alcohol content of the specified portion size. Total alcohol consumption was generated by summing alcohol intake across all alcoholic beverages.

Intake of alcohol as measured by these FFQs has previously been validated [18–20]. In these validation studies, participants of the NHS and HPFS completed the FFQ at one year intervals, during which time they also completed two (HPFS) or four (NHS) one-week dietary records. Correlation coefficients between one-week dietary records and the FFQ were 0.89 for beer, 0.83 for wine, and 0.77 for liquor in NHS and 0.88 for beer, 0.83 for red wine, 0.78 for white wine, and 0.85 for liquor for men [18, 19]. The overall correlation between current alcohol intake reported in the FFQ and multiple 1-week diet records was 0.90 in women and 0.86 in men [20].

In addition, the typical days per week of consuming alcohol was assessed in 1986, 1988, 1996, 2000, and 2004 in NHS, in 1989, 2005, and 2009 in NHSII, and in 1986, 1988, 1998, 2002, 2004, 2006, and 2008 in HPFS. The maximum number of alcoholic beverages consumed was assessed in 1988, 1996, 2000, and 2004 in NHS, in 1989, 2005, and 2009 in NHSII, and in 1988, 1996, 2004, 2006, and 2008 in HPFS. In 1988/9, each cohort asked participants to report their intake of alcohol, in number of beverages per week, at age 18–21.

## Assessment of Covariates

Body mass index (BMI) was calculated using the adult height reported on baseline questionnaires and weight updated every two years in all cohorts. Smoking status was also collected on each questionnaire.

## Identification of Cases

Cases of primary brain malignancy were self-reported on biennial questionnaires, and were subsequently confirmed by medical record review by cohort study investigators. Deaths were identified through the National Death Index, postal authorities, and next-of-kin. For any death that may have been due to a primary brain tumor, we sought medical records to confirm the diagnosis; these records were also used to extract data on tumor subtype, which was categorized as glioblastoma (GBM) vs. non-GBM. Follow-up for mortality through these methods assured nearly complete ascertainment of deaths and their causes [21]. Only cases with confirmed diagnoses were included in this analysis.

## Statistical Analyses

Follow-up was begun at the date of return of the baseline FFQ and continued to the date of diagnosis, death, or the end of follow-up (December 31, 2013 for NHS and NHSII; December 31, 2016 for HPFS), whichever came first. Our primary analyses used the cumulative average of all available FFQs up to that point in time as the exposure. In NHSII, for example, intake for the years 2003–2007 was represented by the average alcohol intake reported in each of the preceding FFQs (1991, 1995, 1999, and 2003), which provided the exposure for the subsequent follow-up period. We excluded from the analyses participants who did not complete the baseline FFQ. If dietary data were missing at any point in a non-baseline questionnaire, responses from the prior FFQ were carried forward up to 8 years, and otherwise set to missing. Secondary analyses included recent intake (for which intake was computed by averaging the two most recent FFQs), baseline intake, and four year lagged intake, which excluded the first four years of follow up.

Analyses were performed for glioma overall and GBM separately in each cohort. Cox proportional hazards models were constructed to estimate hazard ratios (HRs) of glioma and 95% confidence intervals (CIs) by category of alcohol intake, for alcohol intake overall and for specific beverages. Covariates in the models included body mass index (BMI), smoking status, and total caloric intake. BMI was categorized according to World Health Organization definitions as ≤25, 25-<30, and ≥30 kg/m$^2$. Smoking status was also reported on each biennial questionnaire and was categorized as never smoker vs. past smoker vs. current smoker. All models were additionally adjusted for total caloric intake, which minimizes extraneous variation due to underreporting or overreporting in the FFQ [22]. Each of these covariates was updated at each available time point. Age in months was used as the underlying time scale with stratification by calendar time. We additionally analyzed the association between alcohol intake and glioma with mutual adjustment for alcohol from different beverage types (e.g., beer adjusted for red and white wine and liquor).

Categorization of alcohol intake and intake of alcohol from each beverage was based on the distribution of responses observed in the cohorts. Intake was categorized as ≤0.5 grams/day, 0.5–2 g/d, >2–8 g/d, and >8 g/d. These categories approximately correspond to 0–0.25, >0.25–0.75, >0.75–1, >1–4, and >4 servings/week. For total alcohol, additional categories of >8–15 g/d (approximately >4–7.5 servings/week) and >15 g/d were included.

To account for the possibility that some participants in the reference category were current abstainers who were formerly heavy drinkers, we conducted a sensitivity analysis by excluding those participants who reported reducing their intake of alcohol prior to baseline. In NHS and HPFS, at baseline, participants were asked to report if their intake of alcohol had changed in the preceding 10 years; in the sensitivity analysis, we excluded those who reported decreasing alcohol intake and reported ≤0.5 g/d of alcohol intake at baseline. In NHSII, this question was not assessed, so instead, we excluded participants who reported ≤0.5 g/d of intake at baseline in 1991 and who also reported previously consuming >25 average drinks/week at ages 15–17, 18–22, 23–30, or 31–40.

In secondary analyses, we also examined associations between drinking patterns and glioma risk. Responses to these questions on each relevant questionnaire were carried forward until the following assessment; participants who did not respond were marked as missing and did not contribute person-time during those periods. These analyses were adjusted for total alcohol intake using the same categories as above.

We examined whether inclusion of alcohol intake at age 18–21 significantly improved model fit by performing likelihood ratio tests in each cohort using nested models. The full model included total alcohol intake throughout adulthood, alcohol intake at age 18–21, BMI, smoking status, and total caloric intake, while the nested model included all of these variables except alcohol intake at age 18–21.

We did not compute tests of linear trend in glioma risk for increasing categories of alcohol and specific alcoholic beverage intake because of the *a priori* hypothesis of a possible U-shaped or otherwise non-linear association between alcohol intake and glioma incidence. Analyses of the female NHS and NHSII cohorts were combined by meta-analysis using the fixed-effect model. Analyses of all three cohorts were then combined by meta-analysis using the fixed-effect model, and p-heterogeneity was calculated for each measure. All statistical analyses were performed using the SAS 9.4 statistical package (SAS Institute, Cary, NC), and all p-values were derived from two-sided tests. The threshold for significance was set at 0.05.

## Results

In total, 554 incident cases of glioma (343 among women, 211 among men, 362 GBM) were identified among 237,505 total participants with 6,216,378 person-years of follow up (Table 1). A large proportion of each cohort were nondrinkers at baseline (31% in NHS, 42% in NHSII, 24% in HPFS). Average daily alcohol intake was substantially higher in HPFS than NHS or NHSII (11.2 vs. 6.2 vs. 3.0 g/d, respectively).

Overall, cumulative average alcohol intake was associated with reduced risk of glioma (HR=0.75, 95%CI: 0.56–0.99 comparing >8–15 g/d vs. ≤0.5 g/d; HR=0.71, 95%CI: 0.53–0.96 comparing >15 g/d vs. ≤0.5 g/d, Table 2). There was no evidence of significant confounding by BMI or smoking status. Findings for specific alcoholic beverages were generally inverse and non-significant. Overall findings were similar but less precise for GBM, due to smaller case counts.

When stratified by sex (Table 3), the inverse association between alcohol intake and glioma risk was observed in both women and men, though in women the association was statistically significant only at intakes above 15 g/d (HR=0.62, 95%CI: 0.39–0.97 for >15 g/d compared to ≤0.5 g/d). Total wine intake was also associated with reduced risk among women (HR=0.60, 95%CI: 0.37–0.97 comparing >8 to ≤0.5 g/d).

For men, alcohol intake was associated with reduced glioma risk (HR=0.63, 95%CI: 0.43–0.94 for >2–8 and HR=0.57, 95%CI: 0.36–0.89 for >8–15 compared to ≤0.5 g/d); the association was weaker and nonsignificant for alcohol intake exceeding 15 g/dNo clear patterns in the association across intake categories were observed for alcohol from specific alcoholic beverages in men.

Different temporal definitions of alcohol intake resulted in similar overall findings (Table 4). Baseline total alcohol intake (HR=0.75, 95%CI: 0.56–0.99 comparing >8–15 to ≤0.5 g/d) and recent total alcohol intake (HR=0.74, 95%CI: 0.55–0.99 comparing >8–15 to ≤0.5 g/d) were each associated with reduced glioma risk. Hazard ratios were similar though non-significant for four year lagged intake (HR=0.76, 95%CI: 0.56–1.02 comparing >8–15 to ≤0.5 g/d). Associations were weaker and nonsignificant for baseline and recent alcohol intake exceeding 15 g/day, as well as after applying a four-year lag.

In each cohort, addition of alcohol consumption at age 18–21 did not improve model fit (data not shown). P-values for the likelihood ratio test comparing nested models were 0.35 for NHS, 0.10 for HPFS, and 0.88 for NHSII. Mutual adjustment of individual alcoholic beverages for others (i.e., beer adjusted for red and white wine and liquor) yielded similar overall findings (Supplementary Table 1).

Analyses of drinking frequency per week and maximum daily drinks of alcohol showed a nonsignificant increase in glioma risk; of note, case counts in the highest category of >4 maximum drinks per day were limited (n=13). Compared to non-drinkers, the HR among those drinking a maximum of >3–4 drinks/day was HR=1.37, 95%CI: 0.97–1.94 and was HR=1.29, 95%CI: 0.68–2.44 among those drinking >4 maximum drinks/day (Supplementary Table 2).

Exclusion of participants in the reference category who reported reducing their intake of alcohol prior to baseline did not materially change the results (Supplementary Table 3). In this sensitivity analysis, alcohol intake in the range of >8–15 was similarly inversely associated with glioma compared to ≤0.5 g/d (HR=0.71, 95%CI: 0.51–1.00), though not statistically significantly. HRs remained similarly inverse in general, though power was reduced due to exclusion of 64 cases.

## Discussion

In this study, we observed an inverse association between alcohol intake and glioma risk, among both men and women. Results were similar when restricted only to GBM, the most common subtype, and when different temporal classifications of alcohol were used. In the overall analysis, no significant inverse associations were identified between specific alcoholic beverages and glioma risk. Interestingly, inclusion of alcohol consumption in

early adulthood did not improve model fit, suggesting that adult alcohol consumption may be most closely related to glioma risk. Taken in total, the findings reported here provide evidence against a positive association between alcohol intake and glioma risk during adulthood and are consistent with an inverse association at this level of intake.

Alcohol is an identified human carcinogen that penetrates the blood brain barrier and may play a role in development of glioma [23]. Alcohol disrupts DNA methylation,[24] reduces antioxidant levels in the blood,[25] and has been linked to increased risk of several cancers, including those of the liver and breast [4, 5]. On the other hand, moderate alcohol intake is associated with reduced risk of cardiovascular disease and all-cause mortality,[13] a lower risk of stroke,[12] and lower risk of kidney cancer[26] compared to never drinkers and heavy drinkers. Laboratory evidence has also shown that constituents in alcoholic beverages, including xanthohumol, a flavonoid present in beer, and phenols in red wine, may play a role in reducing the growth and development of glioma [27, 28].

The association between alcohol intake and glioma risk has been investigated in more than a dozen case-control studies and several prospective cohort studies. Among case-control studies, several have reported increased risk with higher alcohol consumption,[29–33] although in general these studies did not assess risk by specific beverages, did not stratify by sex, and were at risk of bias due to the method of data collection or control selection. In case-control studies of alcohol intake in particular, the risk of recall bias may be substantial, and this bias may be more challenging in the context of glioma [34]. A recent Mendelian randomization (MR) analysis of 5,739 glioma cases and 5,501 glioma controls identified suggestive evidence for an association between increased alcohol consumption and higher risk of glioma [35]. MR analyses in the context of alcohol are complicated by several factors, however, including pleiotropy, confounding, an inability to distinguish healthier from less healthy drinking patterns (e.g., occasional small consumption vs. binging), and difficulty examining non-linear effects [36].

Prospective cohort studies on the subject have also yielded mixed results, but have tended toward more inverse than positive associations [6, 11, 37]. In the NIH-AARP Diet and Health Study, an analysis including 704 glioma cases identified significant inverse, dose-dependent associations between alcohol and beer intake and glioma risk, but no associations for wine or liquor [6]. A more recent pooled analysis of the NIH-AARP study, Million Women Study, and PLCO study showed an inverse but non-statistically significant association between alcohol intake and glioma risk (RR=0.97, 95%CI: 0.94–1.01 per 10 g/d alcohol), but did not stratify by sex or examine individual alcoholic beverages [11]. Data from the Melbourne Collaborative Cohort study including 67 glioblastoma cases, on the other hand, reported no significant differences for those drinking <20 g/d of alcohol, but a higher risk for those drinking 20–39 g/d (HR=1.79, 95%CI: 0.81–3.95), 40–59 g/d (HR=3.07, 95%CI: 1.26–7.47), and ≥60 g/d (HR=2.54, 95%CI: 0.92–7.00), compared to lifetime abstainers [37].

Strengths of the current study include detailed and repeated assessment of alcohol during adulthood over a long duration of follow-up. This permitted analyses of baseline, cumulatively updated, and recent intake, as well as lagged analyses, to allow assessment

of different temporal associations between alcohol intake and glioma risk. In addition, the large number of participants and relatively large number of accrued glioma cases allowed for subtype analysis (i.e., GBM-only), and stratification by sex. Limitations include the relatively low level and narrow range of alcohol intake, particularly among women, and the fact that the majority of participants were White. Few participants consumed >45 g/d of alcohol in these cohorts, making risk estimates for heavy use less precise and therefore not separately categorized in the current analysis. Future studies that include more heavy alcohol users may demonstrate a non-linear association between alcohol intake and glioma risk, and show an increased risk at higher levels of consumption, such as that reported above 20 g/d in the Melbourne Collaborative Cohort Study [37].

## Conclusion

These results provide evidence against a positive association between alcohol intake during adulthood and glioma risk. Given the relatively low level of alcohol intake in these cohorts, low or moderate alcohol intake may reduce risk of glioma.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgements

We would like to thank the participants and staff of the Nurses' Health Study, Nurses' Health Study II, and Health Professionals Follow Up Study for their valuable contributions as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WY. The authors assume full responsibility for analyses and interpretation of these data.

### Funding

National Institutes of Health (NIH) PO1 CA87969, U01 CA167552, UM1 CA186107, U01 CA176726, UM1 CA167552, F30 CA235791 (DJC), the Nutrition Round Table of the Harvard T.H. Chan School of Public Health, and the H. Lee Moffitt Cancer Center & Research Institute (P30 CA076292).

## Availability of Data/Code

The data and code used in this analysis are available from the corresponding author upon reasonable request.

## References

[1]. Ostrom QT, Cote DJ, Ascha M, Kruchko C, Barnholtz-Sloan JS. Adult Glioma Incidence and Survival by Race or Ethnicity in the United States From 2000 to 2014. JAMA oncology. 2018;4:1254–62. [PubMed: 29931168]

[2]. Barnholtz-Sloan JS, Ostrom QT, Cote D. Epidemiology of Brain Tumors. Neurologic clinics. 2018;36:395–419. [PubMed: 30072062]

[3]. Kim MK, Ko MJ, Han JT. Alcohol consumption and mortality from all-cause and cancers among 1.34 million Koreans: the results from the Korea national health insurance corporation's health examinee cohort in 2000. Cancer causes & control : CCC. 2010;21:2295–302. [PubMed: 20941640]

[4]. Bagnardi V, Blangiardo M, La Vecchia C, Corrao G. A meta-analysis of alcohol drinking and cancer risk. British journal of cancer. 2001;85:1700–5. [PubMed: 11742491]

[5]. Hirko KA, Chen WY, Willett WC, Rosner BA, Hankinson SE, Beck AH, et al. Alcohol consumption and risk of breast cancer by molecular subtype: Prospective analysis of the nurses' health study after 26 years of follow-up. International journal of cancer. 2016;138:1094–101. [PubMed: 26384849]

[6]. Braganza MZ, Rajaraman P, Park Y, Inskip PD, Freedman ND, Hollenbeck AR, et al. Cigarette smoking, alcohol intake, and risk of glioma in the NIH-AARP Diet and Health Study. British journal of cancer. 2014;110:242–8. [PubMed: 24335921]

[7]. Benson VS, Pirie K, Green J, Casabonne D, Beral V. Lifestyle factors and primary glioma and meningioma tumours in the Million Women Study cohort. British journal of cancer. 2008;99:185–90. [PubMed: 18560401]

[8]. 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. Journal of neuro-oncology. 2004;68:57–69. [PubMed: 15174522]

[9]. Hurley SF, McNeil JJ, Donnan GA, Forbes A, Salzberg M, Giles GG. Tobacco smoking and alcohol consumption as risk factors for glioma: a case-control study in Melbourne, Australia. Journal of epidemiology and community health. 1996;50:442–6. [PubMed: 8882229]

[10]. Hochberg F, Toniolo P, Cole P, Salcman M. Nonoccupational risk indicators of glioblastoma in adults. Journal of neuro-oncology. 1990;8:55–60. [PubMed: 2319291]

[11]. Kuan AS, Green J, Kitahara CM, De González AB, Key T, G KR, et al. Diet and risk of glioma: combined analysis of 3 large prospective studies in the UK and USA. Neuro-oncology. 2019;21:944–52. [PubMed: 30690490]

[12]. Jimenez M, Chiuve SE, Glynn RJ, Stampfer MJ, Camargo CA Jr., Willett WC, et al. Alcohol consumption and risk of stroke in women. Stroke. 2012;43:939–45. [PubMed: 22403048]

[13]. Mostofsky E, Mukamal KJ, Giovannucci EL, Stampfer MJ, Rimm EB. Key Findings on Alcohol Consumption and a Variety of Health Outcomes From the Nurses' Health Study. American journal of public health. 2016;106:1586–91. [PubMed: 27459455]

[14]. Mills PK, Preston-Martin S, Annegers JF, Beeson WL, Phillips RL, Fraser GE. Risk factors for tumors of the brain and cranial meninges in Seventh-Day Adventists. Neuroepidemiology. 1989;8:266–75. [PubMed: 2812186]

[15]. Bao Y, Bertoia ML, Lenart EB, Stampfer MJ, Willett WC, Speizer FE, et al. Origin, Methods, and Evolution of the Three Nurses' Health Studies. American journal of public health. 2016;106:1573–81. [PubMed: 27459450]

[16]. Smith-Warner SA, Spiegelman D, Ritz J, Albanes D, Beeson WL, Bernstein L, et al. Methods for pooling results of epidemiologic studies: the Pooling Project of Prospective Studies of Diet and Cancer. American journal of epidemiology. 2006;163:1053–64. [PubMed: 16624970]

[17]. Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. American journal of epidemiology. 1985;122:51–65. [PubMed: 4014201]

[18]. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. American journal of epidemiology. 1992;135:1114–26; discussion 27–36. [PubMed: 1632423]

[19]. Feskanich D, Rimm EB, Giovannucci EL, Colditz GA, Stampfer MJ, Litin LB, et al. Reproducibility and validity of food intake measurements from a semiquantitative food frequency questionnaire. Journal of the American Dietetic Association. 1993;93:790–6. [PubMed: 8320406]

[20]. Giovannucci E, Colditz G, Stampfer MJ, Rimm EB, Litin L, Sampson L, et al. The assessment of alcohol consumption by a simple self-administered questionnaire. American journal of epidemiology. 1991;133:810–7. [PubMed: 2021148]

[21]. Stampfer MJ, Willett WC, Speizer FE, Dysert DC, Lipnick R, Rosner B, et al. Test of the National Death Index. American journal of epidemiology. 1984;119:837–9. [PubMed: 6720679]

[22]. Willett WC. Nutritional Epidemiology. New York: Oxford University Press; 1998.

[23]. Alcohol consumption and ethyl carbamate. IARC monographs on the evaluation of carcinogenic risks to humans. 2010;96:3–1383. [PubMed: 21735939]

[24]. Möllemann M, Wolter M, Felsberg J, Collins VP, Reifenberger G. Frequent promoter hypermethylation and low expression of the MGMT gene in oligodendroglial tumors. International journal of cancer. 2005;113:379–85. [PubMed: 15455350]

[25]. Stryker WS, Kaplan LA, Stein EA, Stampfer MJ, Sober A, Willett WC. The relation of diet, cigarette smoking, and alcohol consumption to plasma beta-carotene and alpha-tocopherol levels. American journal of epidemiology. 1988;127:283–96. [PubMed: 3257350]

[26]. Chow WH, Dong LM, Devesa SS. Epidemiology and risk factors for kidney cancer. Nature reviews Urology. 2010;7:245–57. [PubMed: 20448658]

[27]. Arranz S, Chiva-Blanch G, Valderas-Martínez P, Medina-Remón A, Lamuela-Raventós RM, Estruch R. Wine, beer, alcohol and polyphenols on cardiovascular disease and cancer. Nutrients. 2012;4:759–81. [PubMed: 22852062]

[28]. Festa M, Capasso A, D'Acunto CW, Masullo M, Rossi AG, Pizza C, et al. Xanthohumol induces apoptosis in human malignant glioblastoma cells by increasing reactive oxygen species and activating MAPK pathways. Journal of natural products. 2011;74:2505–13. [PubMed: 22111577]

[29]. 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. International journal of cancer. 1994;59:357–62. [PubMed: 7927941]

[30]. 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 : CCC. 1997;8:13–24. [PubMed: 9051318]

[31]. Hu J, La Vecchia C, Negri E, Chatenoud L, Bosetti C, Jia X, et al. Diet and brain cancer in adults: a case-control study in northeast China. International journal of cancer. 1999;81:20–3. [PubMed: 10077146]

[32]. Boeing H, Schlehofer B, Blettner M, Wahrendorf J. Dietary carcinogens and the risk for glioma and meningioma in Germany. International journal of cancer. 1993;53:561–5. [PubMed: 8436429]

[33]. Ryan P, Lee MW, North B, McMichael AJ. Risk factors for tumors of the brain and meninges: results from the Adelaide Adult Brain Tumor Study. International journal of cancer. 1992;51:20–7. [PubMed: 1563840]

[34]. Barry D Differential recall bias and spurious associations in case/control studies. Statistics in medicine. 1996;15:2603–16. [PubMed: 8961466]

[35]. Howell AE, Robinson JW, Wootton RE, McAleenan A, Tsavachidis S, Ostrom QT, et al. Testing for causality between systematically identified risk factors and glioma: a Mendelian randomization study. BMC cancer. 2020;20:508. [PubMed: 32493226]

[36]. Mukamal KJ, Stampfer MJ, Rimm EB. Genetic instrumental variable analysis: time to call mendelian randomization what it is. The example of alcohol and cardiovascular disease. European journal of epidemiology. 2020;35:93–7. [PubMed: 31761964]

[37]. Baglietto L, Giles GG, English DR, Karahalios A, Hopper JL, Severi G. Alcohol consumption and risk of glioblastoma; evidence from the Melbourne Collaborative Cohort Study. International journal of cancer. 2011;128:1929–34. [PubMed: 21344375]

**Table 1.**

Baseline characteristics of NHS, NHSII, and HPFS participants in analyses of alcohol consumption and glioma risk.

| | NHS | | NHSII | | HPFS | |
|---|---|---|---|---|---|---|
| | Full Cohort (n=92,377) | Cases (n=256) | Full Cohort (n=95,243) | Cases (n=87) | Full Cohort (n=49,885) | Cases (n=211) |
| Age (years, mean, SD) | 46.8 (7.2) | 49.0 (6.7) | 36.6 (4.7) | 37.9 (4.8) | 54.7 (9.8) | 55.7 (8.9) |
| BMI ($kg/m^2$, mean, SD)[a] | 24.4 (4.5) | 24.7 (3.4) | 24.6 (5.3) | 24.7 (2.7) | 24.9 (5.1) | 25.3 (3.4) |
| Smoking status (n, %) | | | | | | |
| Never | 40,023 (43) | 113 (44) | 62,144 (65) | 53 (61) | 22,132 (44) | 95 (45) |
| Past | 25,499 (28) | 84 (33) | 21,210 (22) | 25 (29) | 20,996 (42) | 88 (42) |
| Current | 26,676 (29) | 58 (23) | 11,775 (12) | 8 (9) | 4,811 (10) | 15 (7) |
| Missing | 179 (0) | 1 (0) | 114 (0) | 1 (1) | 1,946 (4) | 13 (6) |
| Race (n, %)[b] | | | | | | |
| White | 65,020 (70) | 130 (51) | 86,906 (91) | 80 (92) | 44,881 (90) | 187 (89) |
| Non-White | 17,008 (18) | 35 (14) | 6,923 (7) | 6 (7) | 2,524 (5) | 10 (5) |
| Missing | 10,349 (11) | 91 (36) | 1,414 (1) | 1 (1) | 2,480 (5) | 14 (6) |
| Overall alcohol intake (g alcohol/d, mean, SD) | | | | | | |
| Total alcohol[a] | 6.2 (10.1) | 6.4 (9.3) | 3.0 (6.0) | 2.2 (2.2) | 11.2 (15.5) | 11.8 (11.1) |
| Beer[a] | 1.2 (5.2) | 1.4 (4.4) | 1.2 (3.6) | 0.9 (1.2) | 3.5 (8.1) | 3.7 (5.5) |
| Red wine[ac] | 0.9 (2.7) | 0.7 (1.5) | 0.3 (1.4) | 0.2 (0.4) | 1.1 (3.1) | 1.5 (2.9) |
| White wine[ac] | 1.9 (4.5) | 1.4 (2.2) | 0.9 (2.6) | 0.6 (0.8) | 1.7 (4.1) | 1.7 (3.0) |
| Total wine[a] | 2.5 (5.4) | 2.1 (3.6) | 1.2 (3.2) | 0.8 (1.0) | 2.8 (5.7) | 3.3 (4.4) |
| Liquor[a] | 2.8 (6.9) | 3.0 (6.1) | 0.6 (2.5) | 0.4 (1.1) | 4.9 (10.4) | 4.9 (8.3) |
| Non-drinkers of (n, %): | | | | | | |
| Any alcohol[a] | 28,854 (31) | 92 (36) | 39,988 (42) | 37 (43) | 11,840 (24) | 64 (30) |
| Beer[a] | 70,947 (77) | 203 (79) | 62,903 (66) | 59 (68) | 22,374 (45) | 106 (50) |
| Red wine[ac] | 56,050 (61) | 163 (64) | 76,214 (80) | 74 (85) | 29,915 (60) | 128 (61) |
| White wine[ac] | 42,783 (46) | 130 (51) | 57,210 (60) | 53 (61) | 22,622 (46) | 105 (50) |
| Total wine[a] | 40,324 (44) | 118 (46) | 53,903 (57) | 50 (57) | 20,309 (41) | 95 (45) |
| Liquor[a] | 51,181 (56) | 139 (54) | 73,910 (78) | 70 (80) | 23,672 (48) | 114 (54) |
| Time to Diagnosis from Baseline (years, mean, SD) | | 16.8 (8.7) | | 13.1 (5.5) | | 13.7 (7.7) |

[a] Age-adjusted.

[b] Available from baseline in NHSII and HPFS, and from 1992 in NHS.

[c] Available from baseline in NHSII and HPFS, and from 1984 in NHS.

Abbreviations: BMI, body mass index; d, day; g, gram; HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; SD, standard deviation;

**Table 2.**

Risk of glioma and glioblastoma in NHS, NHSII, and HPFS by categories of cumulative average total alcohol intake, and separately for alcohol intake from specific beverages.

| | | | All Glioma (n=554) | | | Glioblastoma (n=362) | | |
|---|---|---|---|---|---|---|---|---|
| | Grams Alcohol/Day | Approximate Servings/ Week | Cases | MV HR[ab] | 95%CI | Cases | MV HR[ab] | 95%CI |
| Total Alcohol | 0–0.5 | 0–0.25 | 179 | Ref. | | 115 | Ref. | |
| | >0.5–2 | >0.25–1 | 89 | 0.83 | 0.64–1.07 | 58 | 0.87 | 0.63–1.20 |
| | >2–8 | >1–4 | 137 | 0.85 | 0.68–1.07 | 90 | 0.87 | 0.66–1.16 |
| | >8–15 | >4–7.5 | 69 | 0.75 | 0.56–0.99 | 44 | 0.73 | 0.51–1.05 |
| | >15 | >7.5 | 80 | 0.71 | 0.53–0.96 | 55 | 0.77 | 0.54–1.10 |
| Beer | 0–0.5 | 0–0.25 | 385 | Ref. | | 241 | Ref. | |
| | >0.5–2 | >0.25–1 | 77 | 0.98 | 0.77–1.25 | 58 | 1.00 | 0.75–1.35 |
| | >2–8 | >1–4 | 66 | 1.14 | 0.87–1.51 | 45 | 1.20 | 0.85–1.67 |
| | >8 | >4 | 26 | 1.00 | 0.66–1.52 | 18 | 1.22 | 0.74–2.01 |
| Red Wine | 0–0.5 | 0–0.25 | 357 | Ref. | | 226 | Ref. | |
| | >0.5–2 | >0.25–1 | 117 | 0.96 | 0.77–1.18 | 86 | 1.12 | 0.87–1.44 |
| | >2–8 | >1–4 | 68 | 0.89 | 0.68–1.16 | 38 | 0.77 | 0.54–1.10 |
| | >8 | >4 | 12 | 0.98 | 0.54–1.76 | 12 | 1.46 | 0.80–2.66 |
| White Wine | 0–0.5 | 0–0.25 | 310 | Ref. | | 198 | Ref. | |
| | >0.5–2 | >0.25–1 | 148 | 0.95 | 0.78–1.16 | 103 | 1.05 | 0.82–1.34 |
| | >2–8 | >1–4 | 76 | 0.76 | 0.59–0.98 | 46 | 0.74 | 0.53–1.03 |
| | >8 | >4 | 20 | 0.92 | 0.58–1.45 | 15 | 1.16 | 0.67–1.99 |
| Total Wine | 0–0.5 | 0–0.25 | 247 | Ref. | | 155 | Ref. | |
| | >0.5–2 | >0.25–1 | 154 | 0.99 | 0.80–1.21 | 103 | 1.07 | 0.83–1.38 |
| | >2–8 | >1–4 | 103 | 0.79 | 0.62–1.00 | 67 | 0.82 | 0.61–1.10 |
| | >8 | >4 | 50 | 0.90 | 0.65–1.24 | 37 | 1.04 | 0.71–1.52 |
| Liquor | 0–0.5 | 0–0.25 | 337 | Ref. | | 218 | Ref. | |
| | >0.5–2 | >0.25–1 | 96 | 0.98 | 0.78–1.23 | 59 | 0.94 | 0.70–1.25 |
| | >2–8 | >1–4 | 62 | 0.81 | 0.62–1.08 | 49 | 1.04 | 0.75–1.44 |
| | >8 | >4 | 59 | 0.92 | 0.68–1.24 | 36 | 0.85 | 0.59–1.24 |

[a]Adjusted for age (months), calendar year, smoking status (never vs. past vs. current), BMI (<25 kg/m$^2$ vs. ≥25–<30 kg/m$^2$ vs. ≥30 kg/m$^2$), and total caloric intake (quintiles).

[b]Calculated by fixed effect meta-analysis of all three cohorts. Abbreviations: BMI, body mass index; CI, confidence interval; HPFS, Health Professionals Follow-Up Study; HR, hazard ratio; MV, multivariable; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II;

**Table 3.**

Risk of glioma in NHS, NHSII, and HPFS by categories of cumulative average total alcohol intake, and separately for alcohol intake from specific beverages, stratified by sex.

| | | | Women (n=343) | | | Men (n=211) | | |
|---|---|---|---|---|---|---|---|---|
| | **Grams Alcohol/Day** | **Approximate Servings/ Week** | **Cases** | **MV HR[ab]** | **95%CI** | **Cases** | **MV HR[a]** | **95%CI** |
| Total Alcohol | 0–0.5 | 0–0.25 | 118 | Ref. | | 61 | Ref. | |
| | >0.5–2 | >0.25–1 | 70 | 0.93 | 0.69–1.25 | 19 | 0.58 | 0.35–0.98 |
| | >2–8 | >1–4 | 91 | 1.00 | 0.75–1.32 | 46 | 0.63 | 0.43–0.94 |
| | >8–15 | >4–7.5 | 39 | 0.90 | 0.62–1.30 | 30 | 0.57 | 0.36–0.89 |
| | >15 | >7.5 | 25 | 0.62 | 0.39–0.97 | 55 | 0.79 | 0.53–1.16 |
| Beer | 0–0.5 | 0–0.25 | 266 | Ref. | | 119 | Ref. | |
| | >0.5–2 | >0.25–1 | 39 | 0.90 | 0.64–1.27 | 38 | 1.07 | 0.76–1.51 |
| | >2–8 | >1–4 | 31 | 1.31 | 0.89–1.94 | 35 | 1.00 | 0.67–1.47 |
| | >8 | >4 | 7 | 0.91 | 0.43–1.94 | 19 | 1.04 | 0.63–1.72 |
| Red Wine | 0–0.5 | 0–0.25 | 235 | Ref. | | 122 | Ref. | |
| | >0.5–2 | >0.25–1 | 70 | 0.95 | 0.72–1.24 | 47 | 0.97 | 0.69–1.37 |
| | >2–8 | >1–4 | 35 | 0.85 | 0.59–1.22 | 33 | 0.94 | 0.63–1.40 |
| | >8 | >4 | 3 | 0.52 | 0.17–1.64 | 9 | 1.22 | 0.61–2.44 |
| White Wine | 0–0.5 | 0–0.25 | 197 | Ref. | | 113 | Ref. | |
| | >0.5–2 | >0.25–1 | 86 | 0.95 | 0.74–1.23 | 62 | 0.94 | 0.69–1.29 |
| | >2–8 | >1–4 | 52 | 0.87 | 0.64–1.20 | 24 | 0.57 | 0.36–0.89 |
| | >8 | >4 | 8 | 0.56 | 0.27–1.15 | 12 | 1.30 | 0.71–2.39 |
| Total Wine | 0–0.5 | 0–0.25 | 163 | Ref. | | 84 | Ref. | |
| | >0.5–2 | >0.25–1 | 93 | 0.93 | 0.72–1.20 | 61 | 1.10 | 0.79–1.54 |
| | >2–8 | >1–4 | 68 | 0.90 | 0.67–1.20 | 35 | 0.61 | 0.41–0.92 |
| | >8 | >4 | 19 | 0.60 | 0.37–0.97 | 31 | 1.23 | 0.80–1.88 |
| Liquor | 0–0.5 | 0–0.25 | 225 | Ref. | | 112 | Ref. | |
| | >0.5–2 | >0.25–1 | 58 | 1.00 | 0.74–1.33 | 38 | 0.95 | 0.66–1.39 |
| | >2–8 | >1–4 | 37 | 1.01 | 0.70–1.45 | 25 | 0.59 | 0.38–0.92 |
| | >8 | >4 | 23 | 0.88 | 0.57–1.38 | 36 | 0.95 | 0.64–1.41 |

[a]Adjusted for age (months), calendar year, smoking status (never vs. past vs. current), BMI (<25 kg/m$^2$ vs. ≥25–<30 kg/m$^2$ vs. ≥30 kg/m$^2$), and total caloric intake (quintiles).

[b]Calculated by fixed effect meta-analysis of NHS and NHSII.

Abbreviations: BMI, body mass index; CI, confidence interval; HPFS, Health Professionals Follow-Up Study; HR, hazard ratio; MV, multivariable; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II;

**Table 4.**

Risk of glioma in NHS, NHSII, and HPFS by various temporal classifications of total alcohol intake, and separately for alcohol intake from specific beverages.

| | | | Baseline Intake[a] | | | Cumulative Average Intake | | | Recent Intake[b] | | | Four Year Lag | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Grams Alcohol/Day | Approximate Servings/Week | Cases[c] | MV HR[de] | 95%CI | Cases | MV HR[de] | 95%CI | Cases[c] | MV HR[de] | 95%CI | Cases[c] | MV HR[de] | 95%CI |
| Total Alcohol | 0–0.5 | 0–0.25 | 198 | Ref. | | 179 | Ref. | | 207 | Ref. | | 163 | Ref. | |
| | >0.5–2 | >0.25–1 | 102 | 0.85 | 0.66–1.08 | 89 | 0.83 | 0.64–1.07 | 77 | 0.82 | 0.63–1.07 | 82 | 0.82 | 0.63–1.08 |
| | >2–8 | >1–4 | 102 | 0.81 | 0.64–1.04 | 137 | 0.85 | 0.68–1.07 | 112 | 0.85 | 0.67–1.08 | 124 | 0.89 | 0.70–1.13 |
| | >8–15 | >4–7.5 | 69 | 0.75 | 0.56–0.99 | 69 | 0.75 | 0.56–0.99 | 64 | 0.74 | 0.55–0.99 | 62 | 0.76 | 0.56–1.02 |
| | >15 | >7.5 | 83 | 0.81 | 0.61–1.08 | 80 | 0.71 | 0.53–0.96 | 85 | 0.82 | 0.62–1.08 | 75 | 0.79 | 0.58–1.08 |
| Beer | 0–0.5 | 0–0.25 | 385 | Ref. | | 385 | Ref. | | 376 | Ref. | | 338 | Ref. | |
| | >0.5–2 | >0.25–1 | 99 | 0.86 | 0.68–1.09 | 77 | 0.98 | 0.77–1.25 | 85 | 1.00 | 0.78–1.29 | 82 | 1.01 | 0.78–1.30 |
| | >2–8 | >1–4 | 33 | 0.76 | 0.52–1.09 | 66 | 1.14 | 0.87–1.51 | 59 | 1.18 | 0.88–1.58 | 61 | 1.18 | 0.88–1.57 |
| | >8 | >4 | 37 | 1.02 | 0.71–1.46 | 26 | 1.00 | 0.66–1.52 | 25 | 0.99 | 0.65–1.51 | 25 | 1.04 | 0.68–1.60 |
| Red Wine | 0–0.5 | 0–0.25 | 371 | Ref. | | 357 | Ref. | | 364 | Ref. | | 226 | Ref. | |
| | >0.5–2 | >0.25–1 | 130 | 0.92 | 0.75–1.13 | 117 | 0.96 | 0.77–1.18 | 99 | 0.94 | 0.75–1.18 | 111 | 1.01 | 0.81–1.27 |
| | >2–8 | >1–4 | 27 | 0.77 | 0.52–1.15 | 68 | 0.89 | 0.68–1.16 | 62 | 0.89 | 0.67–1.18 | 55 | 0.86 | 0.64–1.16 |
| | >8 | >4 | 15 | 1.12 | 0.66–1.90 | 12 | 0.98 | 0.54–1.76 | 20 | 0.92 | 0.58–1.48 | 12 | 1.50 | 0.83–2.74 |
| White Wine | 0–0.5 | 0–0.25 | 291 | Ref. | | 310 | Ref. | | 322 | Ref. | | 278 | Ref. | |
| | >0.5–2 | >0.25–1 | 178 | 0.92 | 0.76–1.11 | 148 | 0.95 | 0.78–1.16 | 138 | 1.00 | 0.81–1.22 | 127 | 0.91 | 0.73–1.13 |
| | >2–8 | >1–4 | 45 | 0.69 | 0.50–0.95 | 76 | 0.76 | 0.59–0.98 | 63 | 0.77 | 0.58–1.01 | 80 | 0.91 | 0.71–1.17 |
| | >8 | >4 | 29 | 0.79 | 0.54–1.17 | 20 | 0.92 | 0.58–1.45 | 22 | 0.94 | 0.61–1.47 | 21 | 1.06 | 0.67–1.67 |
| Total Wine | 0–0.5 | 0–0.25 | 265 | Ref. | | 247 | Ref. | | 264 | Ref. | | 232 | Ref. | |
| | >0.5–2 | >0.25–1 | 170 | 0.90 | 0.74–1.10 | 154 | 0.99 | 0.80–1.21 | 136 | 0.95 | 0.77–1.17 | 138 | 0.93 | 0.75–1.15 |
| | >2–8 | >1–4 | 66 | 0.80 | 0.61–1.06 | 103 | 0.79 | 0.62–1.00 | 87 | 0.80 | 0.62–1.02 | 91 | 0.77 | 0.60–0.99 |
| | >8 | >4 | 53 | 0.82 | 0.61–1.11 | 50 | 0.90 | 0.65–1.24 | 58 | 0.86 | 0.64–1.17 | 45 | 0.93 | 0.66–1.29 |
| Liquor | 0–0.5 | 0–0.25 | 325 | Ref. | | 337 | Ref. | | 379 | Ref. | | 312 | Ref. | |
| | >0.5–2 | >0.25–1 | 133 | 1.00 | 0.81–1.23 | 96 | 0.98 | 0.78–1.23 | 65 | 0.84 | 0.64–1.10 | 80 | 0.87 | 0.68–1.12 |
| | >2–8 | >1–4 | 42 | 0.80 | 0.57–1.11 | 62 | 0.81 | 0.62–1.08 | 47 | 0.80 | 0.59–1.09 | 61 | 0.88 | 0.66–1.16 |

| | | | Baseline Intake[a] | | | Cumulative Average Intake | | | Recent Intake[b] | | | Four Year Lag | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Grams Alcohol/Day | Approximate Servings/Week | Cases[c] | MV HR[de] | 95%CI | Cases | MV HR[de] | 95%CI | Cases[c] | MV HR[de] | 95%CI | Cases[c] | MV HR[de] | 95%CI |
| | >8 | >4 | 54 | 0.84 | 0.62–1.14 | 59 | 0.92 | 0.68–1.24 | 54 | 0.92 | 0.68–1.24 | 53 | 0.92 | 0.67–1.25 |

[a]Baseline is 1986 in HPFS, 1991 in NHSII, and 1980 in NHS, except for white/red wine, for which baseline is 1984 in NHS.

[b]Recent intake is the average of the two most recent dietary questionnaire response.

[c]Cases may not sum to total due to missing values.

[d]Adjusted for age (months), calendar year, smoking status (never vs. past vs. current), BMI (<25 kg/m$^2$ vs. ≥25-<30 kg/m$^2$ vs. ≥30 kg/m$^2$), and total caloric intake (quintiles).

[e]Calculated by fixed effect meta-analysis of all three cohorts.

Abbreviations: BMI, body mass index; CI, confidence interval; HPFS, Health Professionals Follow-Up Study; HR, hazard ratio; MV, multivariable; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II;

*Eur J Epidemiol*. Author manuscript; available in PMC 2022 September 04.