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Nonsteroidal Anti-inflammatory Drugs and Glioma in the NIH-AARP Diet and Health Study Cohort

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Abstract

Several case–control studies have suggested that nonsteroidal anti-inflammatory drugs (NSAIDs) reduce risk for glioblastoma, an aggressive form of brain cancer. Prospective investigations have not observed such an association, but these studies lacked adequate brain cancer case numbers and did not stratify by histologic subtype. We prospectively investigated the association between NSAID use and risk of all glioma as well as the risk of glioblastoma subtype in the National Institutes of Health (NIH)-AARP Diet and Health Study. The frequency of aspirin and nonaspirin NSAID use 1 year prior to baseline was ascertained using a self-administered questionnaire. Hazard ratios (HRs) and 95% confidence intervals (CI) were estimated using Cox regression models with age as the underlying time metric, adjusted for sex, race, and history of heart disease. The analysis included 302,767 individuals, with 341 incident glioma cases (264 glioblastoma). No association was observed between regular use (>2 times/wk) of aspirin and risk of glioma (HR=1.16; 95% CI, 0.87–1.56) or glioblastoma (HR=1.17; 95% CI, 0.83–1.64) as compared with no use. Null associations were also observed for nonaspirin NSAID use (HR for glioma = 0.90; 95% CI, 0.65–1.25 and HR for glioblastoma=0.83; 95% CI, 0.56–1.20) as compared with no use. Our findings from this large prospective study do not support an inverse association between NSAIDs and risk of all glioma or glioblastoma.

Introduction

Glioma, the most frequently diagnosed type of primary malignant brain tumor, is highly lethal. The most common histologic subtype, glioblastoma, has a 5-year survival rate of 3.4% despite treatment (1). Interventions that can prevent the development or slow the growth of these tumors are urgently needed.

Case–control studies have suggested that nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit COX-1 and COX-2, may lower the risk for all glioma and specifically for the glioblastoma subtype (2, 3). COX-2, an inducible enzyme, plays a key role in the inflammatory response through the production of prostaglandins and is overex-pressed in

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glioma tissue (4–6), with increasing levels associated with advanced grade of the tumor and poor survival (7, 8). *In vitro* studies have shown that NSAIDs inhibit glioma cell growth through COX-2–dependent (5) and COX-2–independent mechanisms (5, 9–11).

With the exception of one prospective analysis that reported a statistically significant inverse association between aspirin and brain cancer death (12), other prospective epidemiologic studies have found no association (13) or an elevated association (14–17) between NSAIDs and brain cancer incidence or mortality. These analyses were generally limited by modest numbers of brain cancer cases and lacked statistical power to evaluate brain tumors by histologic subtype. Few studies accounted for a lag that would address the possibility of early symptoms of brain cancer influencing the frequency of NSAID use and most of the studies focused primarily on aspirin; only one study to our knowledge has examined nonaspirin NSAIDs and brain cancer (16). Nonaspirin NSAIDs have been shown to be more potent than aspirin at inducing antiproliferative and proapoptotic mechanisms in some cell lines (18, 19) and, therefore, should be evaluated independently of aspirin.

We examined the association of self-reported aspirin and nonaspirin NSAID use with risk of incident glioma in a large prospective cohort. Our study addresses limitations of prior studies by examining both aspirin and nonaspirin NSAIDs and by exploiting our large sample size to examine the most important histologic subtype, glioblastoma.

Materials and Methods

Study design

The NIH-AARP Diet and Health Study is a prospective cohort study of diet and lifestyle factors initiated in 1995 to 1996. A baseline questionnaire was sent to 3.5 million AARP members (50–71 years old) from 6 US states (CA, FL, LA, NJ, NC, and PA) and 2 metropolitan areas (Atlanta, GA, and Detroit, MI) and was returned by 617,119 individuals (17.6%; ref. 20). A second questionnaire, which ascertained NSAID use, was sent in 1996 to 1997 to all participants and was completed by 334,907 individuals (59% of the 566,402 eligible at baseline). Individuals were excluded if they reported a previous cancer at baseline (n = 18,862), had questionnaires filled out by proxies (n = 10,383), or lacked information on both aspirin and nonaspirin NSAID use (n = 2,895).

Assessment of NSAID use

Information on the frequency of NSAID use was obtained by a self-administered questionnaire. The questionnaire asked about the use of aspirin products [During the past 12 months, did you take any of the following aspirin products: Generic aspirin, Bayer, Bufferin, Anacin, Ecotrin, Excedrin (YES/NO)] and also more generally about other nonaspirin NSAIDs [During the past 12 months, did you take any of the following pain relievers: Generic ibuprofen, Advil, Nuprin, Motrin, Aleve, Orudis, Ketoprofen, Naprosyn, Anaprox, Feldene, Piroxicam, Clinoril, Sulindac, Indocin, Indomethacin, Relafen, Nalfon, Nambumetone, or Fenoprofen (YES/NO)]. Frequency of aspirin and non-aspirin NSAID use was assessed among those who reported NSAID use in the past year (If yes, how often did you usually take them? <2 times/mo, 2–3 times/mo, 1–2 times/wk, 3–4 times/wk, 5–6 times/wk, 1 time/d, and ≥2 times/d). Because of the general ascertainment of nonaspirin NSAID use, we were not able to separate out effects of individual formulations of nonaspirin NSAIDs. Participants were specifically instructed not to include Tylenol, acetaminophen, or any other pain relievers in their response.

Brain cancer case ascertainment

Incident cases of primary glioma (ICD-O-3 codes C710-C719, histology code: 9380–9451), including glioblastoma (ICD-O-3 histology codes 9440, 9441, 9442), were ascertained by record linkage to state cancer registries. Previous validation studies for AARP have shown a high level of ascertainment of incident cancer cases (≥90%) from cancer registries (21). Cohort participants were followed on an annual basis for change of address by matching cohort participants with the National Change of Address database maintained by the U.S. Postal Service. Vital status was ascertained though periodic linkage of the cohort to the Social Security Administration (SSA) Death Master File, follow-up searches of the National Death Index Plus for participants matched to the SSA Death Master File, cancer registry linkage, questionnaire responses, and responses to other mailings.

Statistical methods

Hazard ratios (HRs) and 95% confidence intervals (CI) were calculated for the association of aspirin and nonaspirin NSAID use and risk of all glioma and glioblastoma using Cox proportional hazards model with age as the time metric and adjusted for race, gender, and history of heart disease. Follow-up time started at the age of the risk factor questionnaire, when NSAID exposure was ascertained, and ended at the age of glioma diagnosis or age at censoring. Censoring events were diagnosis of any other cancer, death, date when individual moved out of cancer ascertainment area, or end of study (December 31, 2006), whichever occurred first. When we assessed glioblastoma as a histologic subtype, individuals diagnosed with other glioma tumors contributed follow-up time as noncases until their diagnosis. Three categories for frequency of NSAID use were created, no use (referent), nonregular use (≤2 times/wk), and regular use (>2 times/wk), with regular use subdivided into less than daily use (>2–6 times/wk) and daily use (1 time/d or more). Risk estimates were calculated overall and stratified by gender. Heterogeneity across strata was assessed by the likelihood ratio test comparing models with and without the corresponding interaction term.

Tests for linear trend of brain cancer risk with increasing frequency of NSAID use were evaluated among exposed individuals using a likelihood ratio test comparing models with and without the trend variable (<2 times/mo = 1, 2–3 times/mo=2.5, 1–2 times/wk=6, 3–4 times/wk=14, 5–6 times/wk = 22, 1 time/d = 30, ≥2 times/d = 60).

Indicator variables were created for missing values, where appropriate. No variable was missing more than 5% of the data. Medical indication for aspirin and nonaspirin NSAID use (history of heart disease, hypertension, diabetes, or stroke) was evaluated in the multivariate models. After adjusting for history of heart disease, the other medical indications for use did not change the results and, therefore, were not included in the final model. Additional factors, including education, marital status, body mass index, physical activity, and mutual adjustment for aspirin and non-aspirin NSAIDs, were also evaluated in the multivariate models but did not significantly alter the estimates, so they were not included in the final models.

Sensitivity analyses were conducted to evaluate the robustness of the associations observed by combining the nonregular NSAID users with the nonusers in the referent group. This comparison of regular to nonregular NSAID users has been reported in other brain cancer studies (2, 3).

In addition, we evaluated the possibility of early symptoms of brain cancer influencing self-reported use of NSAIDs. To account for changes in associations over time, we established 2 periods (period 1, 0–5.2 years; period 2, >5.2 years) on the basis of the median follow-up time of the glioma cases in the cohort. All individuals entered the first period at age of the

risk factor questionnaire and ended at the age of glioma (or glioblastoma) diagnosis or age at censoring. Censoring events for period 1 were the same as those mentioned for the main analysis, although follow-up time was censored at entry age plus 5.2 years. All individuals who had not yet been censored in period 1 entered into period 2 at entry age plus 5.2 years and were followed until age at diagnosis or age at censoring. Censoring events for period 2 were the same as those in the main analysis, although follow-up time for period 2 went through to the end of study. To optimize the power of the lag analysis, we present regular (>2 times/wk) and nonregular (≤2 times/wk) use with no use as the referent.

Results

The cohort used in this analysis consisted of 302,767 individuals including 341 individuals with incident glioma (227 men, 114 women), of these, 264 individuals had incident glioblastoma (176 men, 88 women; Table 1). Glioma cases had a median follow-up time of 5.2 years, whereas noncases in the analysis had a median follow-up time of 10.1 years, totaling 2,614,267 person-years overall.

One quarter of the respondents reported using aspirin daily or more frequently in the 12 months preceding baseline, whereas nearly 30% of the cohort reported not taking any aspirin at all (Table 1). Nonaspirin NSAID use was less common, with a 10% prevalence of daily or more frequent use, and 43% of participants reporting no nonaspirin NSAID use. Daily aspirin users were more likely to be older, male, white, and have a history of heart disease. Daily users of nonaspirin NSAIDs were less likely to be male.

No significant associations were observed between self-reported regular (HR = 1.17; 95% CI, 0.83–1.64) or non-regular (HR = 1.32; 95% CI, 0.95–1.86) use of aspirin and risk of glioblastoma (Table 2). Moreover, no association was observed for regular (HR=0.83; 95% CI, 0.56–1.20) or nonregular (HR = 1.03; 95% CI, 0.79–1.34) use of nonaspirin NSAIDs and risk of glioblastoma. No trend was observed for either aspirin or nonaspirin NSAIDs (all $P_{trend} \geq 0.57$). Similar null associations were observed with glioma (Table 2).

When we evaluated the robustness of the association between regular aspirin users and risk of brain cancer by expanding the referent group to include nonregular aspirin users, the association with glioblastoma (HR = 0.99; 95% CI, 0.76–1.29) was closer to the null. The associations between regular use of nonaspirin NSAIDs and risk of glioblastoma (HR = 0.81; 95% CI, 0.56–1.16) did not change substantially.

Although the case numbers were small ($n = 77$), we also evaluated the association between aspirin and nonaspirin NSAIDs and glioma other than glioblastoma. No significant associations with other glioma tumors were observed for regular aspirin use (HR = 1.16; 95% CI, 0.64–2.09) or for regular nonaspirin NSAID use (HR = 1.20; 95% CI, 0.63–2.30).

In analysis stratified by gender, an elevated association with glioblastoma among the nonregular aspirin users was present among female participants only (glioblastoma male: HR = 1.01; 95% CI, 0.67–1.51; glioblastoma female: HR = 1.93; 95% CI, 1.13–3.28; Table 3). The differences in association between all 3 levels of frequency of aspirin and risk of glioblastoma by gender, however, were not statistically significant ($P_{interaction} = 0.54$). No differences by gender were found for the association between nonaspirin NSAIDs and glioblastoma ($P_{interaction} = 0.19$).

To account for the possibility that early brain cancer symptoms may influence the frequency with which NSAIDs are taken, we evaluated the association between aspirin and nonaspirin NSAIDs and risk of glioblastoma by the median follow-up time among the glioblastoma cases. A non-significant elevation between aspirin and risk of glioblastoma was observed in

the second period for nonregular (HR = 1.48; 95% CI, 0.92–2.37) compared with nonusers of aspirin (Table 4). No associations with aspirin or non-aspirin NSAIDs were observed with risk of all glioma in either period.

Discussion

While experimental evidence and a few epidemiologic studies have suggested a potential chemopreventive role for NSAIDs in brain cancer, we found no evidence of an inverse association between regular use of NSAIDs and risk of glioblastoma. This large prospective analysis addresses the limitations of prior prospective studies by examining both aspirin and nonaspirin NSAIDs separately and by using our large sample size to examine the most important histologic subtype glioblastoma.

Our findings are generally consistent with the findings from other cohort studies on brain cancer incidence and death. All prospective studies, except the study of Rothwell and colleagues (12), have reported either an elevation in risk (14–17) or no association (13) with use of NSAIDs. Most of the previously published cohort studies, because of their small number of cases, were limited in their ability to conduct a lag analysis to account for early symptoms of disease. One prescription-based study of aspirin and brain cancer incidence in Denmark, however, did stratify by follow-up time and attributed the elevation in risk for brain cancer to confounding by indication based on the observation that individuals were prescribed low-dose aspirin after being misdiagnosed with thrombotic cerebral disease (a symptom caused by some brain tumors; ref. 17). The investigation by Friis and colleagues provides evidence that there may be a spectrum of symptoms caused by brain tumors that are commonly treated with aspirin and emphasizes the limitations in interpretation of those results from cohort studies that did not account for this type of bias. The elevation in risk observed in this study between aspirin and glioblastoma in nonregular female users is likely due to confounding by indication, although we do not have any information on preclinical symptoms such as frequency of headaches/migraines to investigate this hypothesis. Alternatively, the elevated association among females may be due to chance.

The length of time between preclinical symptoms and diagnosis of brain cancer is unknown. A long preclinical phase for glioma has been suggested by several other studies evaluating the temporal patterns in the association between epilepsy and risk of glioma where very large associations last for more than a decade before attenuating (22–24). Although some high-grade gliomas might be expected to have a short preclinical phase, one study found little difference in associations for epilepsy by glioma tumor type, suggesting that even high-grade gliomas may have an extended preclinical phase (24). Our findings with aspirin suggest preclinical symptoms may be present more than 5 years before diagnosis.

Despite conducting a lag analysis, our results, particularly for aspirin, do not support an inverse association with glioblastoma even though 2 case–control studies have reported a strong inverse association between regular use of NSAIDs and glioblastoma and a slightly weaker inverse signal with all glioma (2, 3). A pooled study, including data from the 2 previously published case–control studies, also reported an inverse association with glioblastoma, although the protective association was found primarily among those who reported short-term use (<10 years) and had no history of asthma or allergy, whereas no association was found overall with glioma among those who reported any history of asthma and allergy (3). Although history of asthma and allergy has been shown to reduce risk for glioma in multiple studies (25–29), we did not have any information on history of asthma or allergy to evaluate the putative interaction with NSAIDs. One of the major limitations of case–control studies is the potential for recall bias. This type of bias is of particular concern when studying brain cancer because the tumor can cause cognitive impairment and memory

loss and, therefore, result in an underestimation of exposure among cases. Although Sivak-Sears and colleagues did not observe a systematic underestimation of medication use, this type of bias cannot be entirely ruled out for the reporting of NSAIDs. Interestingly, acetaminophen, which is not an NSAID, was found to be as protective as the other NSAIDs for glioblastoma (2), suggesting that some recall bias may have been present.

Two randomized clinical trials have also reported on aspirin and brain cancer: the Women's Health Study, which did not find an association with low-dose aspirin taken every other day and risk of brain cancer (HR=1.21; 95% CI, 0.60–2.46; ref. 13), and a pooled evaluation of multiple randomized trials for daily aspirin use that reported a statistically significant inverse association with death due to brain cancer among participants randomized to aspirin for at least 5 years (HR = 0.31; 95% CI, 0.11–0.89), although the protective association was only apparent for the first 10 years (HR after 10 years = 1.16; 95% CI, 0.49–2.77; ref. 12). In both reports, the number of cases was very small, thus preventing definitive conclusions.

Nondifferential misclassification of NSAIDs due to the self-reported nature of the exposure may have attenuated our results. While some underreporting of NSAID use has been noted, reporting accuracy tends to improve with more frequent and regular use (30, 31). Further misclassification may have occurred because of NSAIDs only being ascertained at baseline and not updated during follow-up time. This one-time exposure ascertainment assumes no change in baseline exposure over time and, therefore, may have further attenuated our findings toward the null. Moreover, we had no information on duration of use which inhibits our ability to further classify individuals into subgroups by short- and long-term use and to evaluate a critical window within which NSAIDs may operate to reduce risk for glioma.

The NIH-AARP cohort study participants are more likely to have attended college or graduate school, be of non-Hispanic white race, and report better overall health status than the general U.S. population. The prevalence of regular NSAID use in the NIH-AARP study, however, has been shown to be comparable with other cohorts with similar age distributions. In addition, associations between NSAIDs and other cancer sites generated by the NIH-AARP cohort study are similar to published findings from other cohort studies. So, while the response rates may have affected the generalizability of the study, it is unlikely to have influenced the internal validity of the results.

Despite these limitations, this is the largest cohort study to date to assess the relationship between NSAIDs and glioma and the first cohort to evaluate risk of glioblastoma separately. Our data do not support a protective effect of NSAIDs overall. Future results from randomized clinical trials of aspirin and nonaspirin NSAIDs with a substantial number of glioma outcomes will be useful in clarifying the relationship between use of NSAIDs and risk of glioma.

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References

1. Central Brain Tumor Registry of the United States (CBTRUS). CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2004–2006. Central Brain Tumor Registry of the United States; Hinsdale, IL: 2010.
2. Sivak-Sears NR, Schwartzbaum JA, Miike R, Moghadassi M, Wrensch M. Case-control study of use of nonsteroidal antiinflammatory drugs and glioblastoma multiforme. Am J Epidemiol. 2004; 159:1131–9. [PubMed: 15191930]
3. Scheurer ME, El-Zein R, Thompson PA, Aldape KD, Levin VA, Gilbert MR, et al. Long-term anti-inflammatory and antihistamine medication use and adult glioma risk. Cancer Epidemiol Biomarkers Prev. 2008; 17:1277–81. [PubMed: 18483351]
4. Deininger MH, Schluesener HJ. Cyclooxygenases-1 and -2 are differentially localized to microglia and endothelium in rat EAE and glioma. J Neuroimmunol. 1999; 95:202–8. [PubMed: 10229132]
5. Joki T, Heese O, Nikas DC, Bello L, Zhang J, Kraeft SK, et al. Expression of cyclooxygenase 2 (COX-2) in human glioma and *in vitro* inhibition by a specific COX-2 inhibitor, NS-398. Cancer Res. 2000; 60:4926–31. [PubMed: 10987308]
6. Buccoliero AM, Caldarella A, Gheri CF, Taddei A, Paglierani M, Pepi M, et al. Inducible cyclooxygenase (COX-2) in glioblastoma-clinical and immunohistochemical (COX-2-VEGF) correlations. Clin Neuropathol. 2006; 25:59–66. [PubMed: 16550738]
7. Perdiki M, Korkolopoulou P, Thymara I, Agrogiannis G, Piperi C, Boviatsis E, et al. Cyclooxygenase-2 expression in astrocytomas. Relationship with microvascular parameters, angiogenic factors expression and survival. Mol Cell Biochem. 2007; 295:75–83. [PubMed: 16868662]
8. Shono T, Tofilon PJ, Bruner JM, Owolabi O, Lang FF. Cyclooxygenase-2 expression in human gliomas: prognostic significance and molecular correlations. Cancer Res. 2001; 61:4375–81. [PubMed: 11389063]
9. Ishibashi M, Bottone FG Jr, Taniura S, Kamitani H, Watanabe T, Eling TE. The cyclooxygenase inhibitor indomethacin modulates gene expression and represses the extracellular matrix protein laminin gamma1 in human glioblastoma cells. Exp Cell Res. 2005; 302:244–52. [PubMed: 15561105]
10. Chuang HC, Kardosh A, Gaffney KJ, Petasis NA, Schonthal AH. COX-2 inhibition is neither necessary nor sufficient for celecoxib to suppress tumor cell proliferation and focus formation *in vitro*. Mol Cancer. 2008; 7:38. [PubMed: 18485224]
11. Wakimoto N, Wolf I, Yin D, O'Kelly J, Akagi T, Abramovitz L, et al. Nonsteroidal anti-inflammatory drugs suppress glioma via 15-hydroxyprostaglandin dehydrogenase. Cancer Res. 2008; 68:6978–86. [PubMed: 18757412]
12. Rothwell PM, Fowkes FG, Belch JF, Ogawa H, Warlow CP, Meade TW. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet. 2011; 377:31–41. [PubMed: 21144578]
13. Cook NR, Lee IM, Gaziano JM, Gordon D, Ridker PM, Manson JE, et al. Low-dose aspirin in the primary prevention of cancer: the Women's Health Study: a randomized controlled trial. JAMA. 2005; 294:47–55. [PubMed: 15998890]
14. Thun MJ, Namboodiri MM, Calle EE, Flanders WD, Heath CW Jr. Aspirin use and risk of fatal cancer. Cancer Res. 1993; 53:1322–27. [PubMed: 8443812]

15. Ratnasinghe LD, Graubard BI, Kahle L, Tangrea JA, Taylor PR, Hawk E. Aspirin use and mortality from cancer in a prospective cohort study. Anticancer Res. 2004; 24:3177–84. [PubMed: 15510608]

16. Sorensen HT, Friis S, Norgard B, Mellemkjaer L, Blot WJ, McLaughlin JK, et al. Risk of cancer in a large cohort of nonaspirin NSAID users: a population-based study. Br J Cancer. 2003; 88:1687–92. [PubMed: 12771981]

17. Friis S, Sorensen HT, McLaughlin JK, Johnsen SP, Blot WJ, Olsen JH. A population-based cohort study of the risk of colorectal and other cancers among users of low-dose aspirin. Br J Cancer. 2003; 88:684–8. [PubMed: 12618874]

18. Takada Y, Bhardwaj A, Potdar P, Aggarwal BB. Nonsteroidal anti-inflammatory agents differ in their ability to suppress NF-kappaB activation, inhibition of expression of cyclooxygenase-2 and cyclin D1, and abrogation of tumor cell proliferation. Oncogene. 2004; 23:9247–58. [PubMed: 15489888]

19. Andrews J, Djakiew D, Krygier S, Andrews P. Superior effectiveness of ibuprofen compared with other NSAIDs for reducing the survival of human prostate cancer cells. Cancer Chemother Pharmacol. 2002; 50:277–84. [PubMed: 12357301]

20. Schatzkin A, Subar AF, Thompson FE, Harlan LC, Tangrea J, Hollenbeck AR, et al. Design and serendipity in establishing a large cohort with wide dietary intake distributions: the National Institutes of Health-American Association of Retired Persons Diet and Health Study. Am J Epidemiol. 2001; 154:1119–25. [PubMed: 11744517]

21. Michaud DS, Midthune D, Hermansen S, Leitzmann M, Harlan LC, Kipnis V, et al. Comparison of cancer registry case ascertainment with SEER estimates and self-reporting in a subset of the NIH-AARP Diet and Health Study. J Regist Manag. 2005; 32:70–75.

22. Olsen JH, Boice JD Jr, Jensen JP, Fraumeni JF Jr. Cancer among epileptic patients exposed to anticonvulsant drugs. J Natl Cancer Inst. 1989; 81:803–8. [PubMed: 2716074]

23. Schlehofer B, Blettner M, Preston-Martin S, Niehoff D, Wahrendorf J, Arslan A, et al. Role of medical history in brain tumour development. Results from the international adult brain tumour study. Int J Cancer. 1999; 82:155–60. [PubMed: 10389745]

24. Schwartzbaum J, Jonsson F, Ahlbom A, Preston-Martin S, Malmer B, Lonn S, et al. Prior hospitalization for epilepsy, diabetes, and stroke and subsequent glioma and meningioma risk. Cancer Epidemiol Biomarkers Prev. 2005; 14:643–50. [PubMed: 15767344]

25. McCarthy BJ, Rankin K, Il'yasova D, Erdal S, Vick N, Ali-Osman F, et al. Assessment of type of allergy and antihistamine use in the development of glioma. Cancer Epidemiol Biomarkers Prev. 2011; 20:370–78. [PubMed: 21300619]

26. Linos E, Raine T, Alonso A, Michaud D. Atopy and risk of brain tumors: a meta-analysis. J Natl Cancer Inst. 2007; 99:1544–50. [PubMed: 17925535]

27. Wiemels JL, Wiencke JK, Sison JD, Miike R, McMillan A, Wrensch M. History of allergies among adults with glioma and controls. Int J Cancer. 2002; 98:609–15. [PubMed: 11920623]

28. Schoemaker MJ, Swerdlow AJ, Hepworth SJ, McKinney PA, van TM, Muir KR. History of allergies and risk of glioma in adults. Int J Cancer. 2006; 119:2165–72. [PubMed: 16823851]

29. Wigertz A, Lonn S, Schwartzbaum J, Hall P, Auvinen A, Christensen HC, et al. Allergic conditions and brain tumor risk. Am J Epidemiol. 2007; 166:941–50. [PubMed: 17646205]

30. West SL, Savitz DA, Koch G, Sheff KL, Strom BL, Guess HA, et al. Demographics, health behaviors, and past drug use as predictors of recall accuracy for previous prescription medication use. J Clin Epidemiol. 1997; 50:975–80. [PubMed: 9291884]

31. Pit SW, Byles JE, Cockburn J. Accuracy of telephone self-report of drug use in older people and agreement with pharmaceutical claims data. Drugs Aging. 2008; 25:71–80. [PubMed: 18184031]

In Memoriam

In memoriam for Dr. Arthur Schatzkin, a visionary investigator who founded the NIH-AARP Diet and Health Study.

Table 1

Demographic characteristics by frequency of aspirin and nonaspirin NSAID use, NIH-AARP, 1996–2006

	Aspirin				Nonaspirin NSAIDs			
	No use	**≤2 times/wk**	**>2–6 times/wk**	**Daily +**	**No use**	**≤2 times/wk**	**>2–6 times/wk**	**Daily +**
Cohort, *n* (%)	80,879 (26.7)	114,805 (38.0)	28,891 (9.5)	75,634 (25.0)	130,928 (43.2)	119,762 (39.6)	18,311 (6.1)	30,616 (10.1)
Median age (interquartile range)	63.5 (58.7–67.4)	62.4 (57.8–66.7)	63.5 (58.8–67.3)	64.7 (60.2–68.0)	64.5 (59.8–67.9)	62.3 (57.6–66.6)	62.4 (57.8–66.6)	63.8 (59.1–67.5)
Gender (% male)	46.9	57.4	62.3	70.8	62.0	59.2	48.5	46.0
Race (% white)	90.1	92.6	94.0	94.3	91.9	93.1	92.7	92.5
History of heart disease	9.7	4.7	10.2	33.3	15.9	11.4	11.5	14.9

Table 2

Frequency of aspirin and nonaspirin NSAID use and risk of incident glioma and glioblastoma, NIH-AARP, 1996–2006

	Case	HR[a] (95%CI)	HR[b] (95%CI)
Glioma			
Aspirin[c]			
No use	75	1.00 (Ref)	1.00 (Ref)
Nonregular	135	1.27 (0.96–1.68)	1.21 (0.91–1.61)
Regular	127	1.31 (0.98–1.74)	1.16 (0.87–1.56)
>2–6 times/wk	31	1.15 (0.77–1.75)	1.07 (0.70–1.62)
7+ times/wk	96	1.37 (1.01–1.86)	1.21 (0.88–1.65)
P_{trend}			0.66
Nonaspirin NSAID[d]			
No use	149	1.00 (Ref)	1.00 (Ref)
Nonregular	141	1.05 (0.83–1.32)	1.06 (0.84–1.33)
Regular	47	0.85 (0.62–1.19)	0.90 (0.65–1.25)
>2–6 times/wk	17	0.83 (0.50–1.38)	0.87 (0.53–1.44)
7+ times/wk	30	0.87 (0.59–1.28)	0.92 (0.62–1.36)
P_{trend}			0.59
Glioblastoma			
Aspirin[c]			
No use	56	1.00 (Ref)	1.00 (Ref)
Nonregular	108	1.36 (0.98–1.88)	1.30 (0.94–1.80)
Regular	96	1.32 (0.95–1.84)	1.17 (0.83–1.64)
>2–6 times/wk	23	1.14 (0.70–1.86)	1.06 (0.65–1.72)
7+ times/wk	73	1.39 (0.98–1.98)	1.21 (0.84–1.75)
P_{trend}			0.57
Nonaspirin NSAID[d]			
No use	118	1.00 (Ref)	1.00 (Ref)
Nonregular	109	1.03 (0.79–1.33)	1.03 (0.79–1.34)
Regular	34	0.78 (0.53–1.14)	0.82 (0.56–1.20)
>2–6 times/wk	9	0.56 (0.28–1.10)	0.58 (0.30–1.15)
7+ times/wk	25	0.91 (0.59–1.41)	0.96 (0.62–1.49)
P_{trend}			0.87

[a] Age as time metric.

[b] Adjusting for sex, race, and history of heart disease using age as time metric.

[c] Four glioblastoma cases were missing for aspirin.

[d] Three glioblastoma cases and 1 glioma case were missing for nonaspirin NSAIDs.

Table 3

Frequency of aspirin and nonaspirin NSAID use and risk of glioma and glioblastoma by gender, NIH-AARP, 1996–2006

	Male		Female	
	Case	HR[a] (95%CI)	Case	HR[a] (95%CI)
Glioma				
Aspirin[b]				
No use	45	1.00 (Ref)	30	1.00 (Ref)
Nonregular	82	1.01 (0.70–1.46)	53	1.60 (1.02–2.50)
Regular	100	1.17 (0.82–1.67)	27	1.05 (0.62–1.77)
>2–6 times/wk	20	0.90 (0.53–1.52)	11	1.42 (0.71–2.83)
7+ times/wk	80	1.28 (0.88–1.86)	16	0.88 (0.47–1.63)
$P_{interaction}$				0.30
Nonaspirin NSAID[c]				
No use	99	1.00 (Ref)	50	1.00 (Ref)
Nonregular	101	1.16 (0.88–1.54)	40	0.86 (0.57–1.31)
Regular	23	0.83 (0.53–1.30)	24	0.95 (0.58–1.54)
>2–6 times/wk	7	0.65 (0.30–1.41)	10	1.11 (0.56–2.19)
7+ times/wk	16	0.94 (0.55–1.59)	14	0.86 (0.48–1.56)
$P_{interaction}$				0.35
Glioblastoma				
Aspirin[b]				
No use	36	1.00 (Ref)	20	Ref
Nonregular	65	1.01 (0.67–1.51)	43	1.93 (1.13–3.28)
Regular	75	1.08 (0.72–1.62)	21	1.23 (0.66–2.28)
>2–6 times/wk	16	0.90 (0.50–1.62)	7	1.35 (0.57–3.19)
7+ times/wk	59	1.15 (0.75–1.76)	14	1.17 (0.59–2.35)
$P_{interaction}$				0.54
Non-aspirin NSAID[c]				
No use	78	1.00 (Ref)	40	1.00 (Ref)
Nonregular	80	1.17 (0.85–1.60)	29	0.78 (0.48–1.26)
Regular	15	0.68 (0.39–1.19)	19	0.94 (0.54–1.62)
>2–6 times/wk	3	0.35 (0.11–1.23)	6	0.83 (0.35–1.97)
7+ times/wk	12	0.89 (0.49–1.64)	13	1.00 (0.53–1.87)
$P_{interaction}$				0.19

[a]Adjusting for race, sex, and history of heart disease using age as time metric.

[b]Four female glioblastoma cases were missing for aspirin.

[c]Three male glioblastoma cases and 1 male glioma case were missing for nonasprin NSAIDs.

Table 4

Regular and nonregular NSAID use and risk of glioma and glioblastoma by length of follow-up, NIH-AARP, 1996–2006

	≤ 5.2 y		>5.2 y	
	Case (*n*)	**HR[a] (95% CI)**	**Case (*n*)**	**HR[a] (95% CI)**
Glioma				
Aspirin[b]				
No use	40	1.00 (Ref)	35	1.00 (Ref)
Nonregular	68	1.18 (0.80–1.75)	67	1.25 (0.83–1.89)
Regular	64	1.02 (0.68–1.54)	63	1.34 (0.88–2.05)
Nonaspirin NSAIDs[c]				
No use	79	1.00 (Ref)	70	1.00 (Ref)
Nonregular	68	0.99 (0.71–1.37)	73	1.12 (0.80–1.56)
Regular	24	0.89 (0.55–1.39)	23	0.92 (0.57–1.48)
Glioblastoma				
Aspirin[b]				
No use	31	1.00 (Ref)	25	1.00 (Ref)
Nonregular	51	1.15 (0.73–1.80)	57	1.48 (0.92–2.37)
Regular	47	0.95 (0.60–1.53)	49	1.45 (0.89–2.38)
Nonaspirin NSAIDs[c]				
No use	61	1.00 (Ref)	57	1.00 (Ref)
Nonregular	50	0.95 (0.65–1.38)	59	1.09 (0.76–1.58)
Regular	18	0.86 (0.51–1.45)	16	0.78 (0.44–1.36)

[a] Adjusting for race, sex, and history of heart disease using age as time metric.

[b] Four glioblastoma cases were missing for aspirin.

[c] Three glioblastoma cases and 1 glioma case were missing for nonaspirin NSAIDs.