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# Statin use, hyperlipidemia, and risk of glioma

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## Abstract

**Background—**Statins have previously been shown to have protective effects for other cancers, but no prospective studies of statin use and glioma have been conducted.

**Methods—**We evaluated the association between statin use and risk of glioma in the female Nurses' Health Study (NHS, n = 114,419) and Nurses' Health Study II (NHSII, n = 115,813) and the male Health Professionals Follow-up Study (HPFS, n = 50,223). Glioma cases were confirmed by medical record review. Age and multivariable-adjusted hazard ratios of glioma by statin use were estimated using Cox proportional hazards models.

**Results—**In 4,430,700 person-years of follow-up, we confirmed 483 incident cases of glioma. Compared with never-users, ever statin use was associated with borderline increased risk of glioma in the combined cohorts (age-adjusted HR = 1.23, 95% CI 0.99–1.54), as was longer duration of statin use (HR = 1.48, 95% CI 1.08–2.03 comparing > 8 years of use to never use, p-trend = 0.01). We also observed a significant inverse association between hyperlipidemia and glioma in multivariable models (HR = 0.74, 95% CI 0.59–0.93 in combined cohorts), which was attenuated in lagged analyses. Compared to never use, in multivariable-adjusted models, ever statin use (HR = 1.43, 95% CI 1.10–1.86) and statin use duration (HR = 1.72, 95% CI 1.21–2.45, for > 8 years of use, p-trend = 0.003) were each significantly associated with increased glioma risk.

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Compliance with ethical standards

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**Conclusion—**In contrast to case–control studies reporting inverse associations, we found borderline increased risk of glioma with statin use. Results were strengthened after adjustment for cardiovascular risk factors due to an unexpected inverse association between hyperlipidemia and glioma risk. Further studies of statin use, hyperlipidemia, and glioma risk are warranted.

### Keywords

Statin; Epidemiology; Glioblastoma multiforme; Glioma; Incidence

## Introduction

Since their introduction in the late 1980s, hydroxy-methylglutaryl-coenyzme A (HMG co-A) reductase inhibitors, or statins, have become one of the most widely used medications, growing rapidly in popularity due to their lack of side effects, efficacy in lowering serum cholesterol, and reduction of cardiovascular risk to become the most commonly prescribed anti-cholesterol medication [1–3]. Based on data from the 2011 to 2012 National Health and Nutrition Examination, an estimated 38.6 million Americans were currently taking statins, more than 10% of the total U.S. population, and approximately 25% of the population over age 45 [4].

Although statins were introduced for prevention of coronary artery disease, increasing evidence suggests a variety of additional health benefits, including possibly reduced risk of Parkinson's disease [5], renal cell carcinoma [6], and lethal prostate cancer [7, 8]. Although their primary use is to lower cholesterol [1], much research has investigated the possibility that statins may lower the incidence of neurological disease [9, 10], may have independent anticancer effects [11, 12], and may reduce inflammation, including specific reductions in brain inflammation [13–15]. In animal models, statins have displayed antitumor effects against glioma, neuroblastoma, lymphoma, pancreatic adenocarcinoma, and melanoma, among other tumors [12]. Statins can reduce proliferation, increase apoptosis, and inhibit overall growth and migration of glioma cells, providing possible mechanisms for an anti-tumor effect of statin use on glioma [16–19]. Statins may also lower brain inflammation, which could contribute to reduced risk of malignant transformation [9, 10].

Three case–control studies have examined the association between statin use and risk of glioma [20–22]. All three studies reported approximately 25% reduction in glioma risk with statin use, although definitions of statin use varied across studies. Two studies also suggested a duration-response relationship, with lowest risk of glioma among those who had used statins the longest [20, 21].

The objective of this study was to analyze the association between statin use and glioma risk in three large, prospective cohort studies. We examined current and ever statin use, as well as duration of use. We further performed lagged analyses to assess whether timing of statin use was associated with glioma risk, and we additionally considered potential confounding of associations by cardiovascular disease risk factors (i.e., hyperlipidemia, hypertension, diabetes, body mass index (BMI), and smoking status). Based on previous studies, our hypothesis was that statin use would be inversely related to glioma risk, in a duration dependent manner.

## Methods

### Study participants

The methods of the NHS, NHSII, and HPFS have been described in detail previously [23–25]. NHS began in 1976 with 121,701 female nurses aged 30–55 years; HPFS began in 1986, with 51,529 male health professionals aged 40–75 years; NHSII began in 1989 with 116,686 female nurses aged 25–42 years. In each cohort, participants completed a baseline questionnaire and subsequent biennial follow-up questionnaires assessed updated information. Follow-up rates in the cohorts have exceeded 90% [26]. The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard T. H. Chan School of Public Health, and those of participating registries as required.

### Assessment of statin use and other covariates

Anti-cholesterol medications were first assessed in 1990 in HPFS, 1994 in NHS, and 1999 in NHSII, and then every 2 years subsequently. Initially, the HPFS and NHS questionnaires asked generally about anti-cholesterol medications, however, in 2000 both cohorts updated the questionnaires to include separate questions for statins and other cholesterol-lowering medications. NHSII questionnaires included a specific question for statins beginning in 2001. Thereafter, biennial follow-up questionnaires in all three cohorts included a question on statins. Therefore, in the main analyses, use of any cholesterol-lowering medication during follow-up (i.e., after 1990), was considered statin use. Participants who did not respond to the anti-cholesterol medication question on the questionnaire before 2000 in HPFS and NHS or 2001 in NHSII or the statin use question thereafter but completed the remainder of the survey were categorized as non-users. Duration of use of statins was estimated by summing use across each 2-year period encompassed by the follow-up questionnaires. In one analysis, duration of use was categorized as never use, 0–4 years, and > 4 years of use; in a separate analysis, the categories were never use, 0–4 years, > 4–8 years, and > 8 years.

Statin type was assessed initially in 2004 in NHS and HPFS, and in 2005 in NHSII. Each questionnaire from those cycles forward asked participants to report the brand of statin they used as Crestor® (rosuvastatin), Pravachol® (pravastatin), Mevacor® (lovastatin), Zocor® (simvastatin), Lipitor® (atorvastatin), or other. In a subgroup analysis, beginning at the time of first assessment of statin type, these were classified as hydrophilic (rosuvastatin and pravastatin) or lipophilic (lovastatin, simvastatin, atorvastatin). We hypothesized that lipophilic statins would have greater penetrance of the blood brain barrier and have a stronger association with glioma risk [9]. We also performed an analysis of ever statin use from these dates forward, irrespective of statin type, as a sensitivity analysis. Risk associations for statin use were also evaluated with explicit questions on their use beginning in 2000 in HPFS and NHS and 2001 in NHSII; this allowed us to examine the assumption that anti-cholesterol medications from 1990 onward were comprised mainly of statins and that use of the broader definition of anti-cholesterol medication had no material influence on study results.

Because statins are prescribed to lower coronary risk due to hyperlipidemia, we also assessed the association between cardiovascular risk factors and glioma risk, including hyperlipidemia, hypertension, diabetes, smoking status, and BMI. Each of these variables was self-reported by participants on every biennial questionnaire for the duration of follow-up. If an individual reported hyperlipidemia, hypertension, or diabetes, they were considered to have that risk factor for the remainder of follow-up. For BMI and smoking status, simple updating at each 2-year follow-up period was used, with values carried forward up to two cycles (4 years) in the case of missing data. Previous validation studies of self-reported hypertension and weight showed high correlation in each cohort (r = 0.97 for both men and women for weight) [27–30].

## Identification of cases

All primary brain malignancy cases were either self-reported on biennial questionnaires and then confirmed by medical record review, or determined by medical record review after death occurred. Therefore, we included only cases that were validated by direct medical record review. Only cases with confirmed ICD-9-CM diagnoses of 191.x, which indicates malignant neoplasm of the brain, were included in this analysis, from which we limited to glioma cases. Deaths were identified mainly through reports from the postal service and next-of-kin; we searched the National Death Index for deaths among non-respondents to follow-up questionnaires. In validation studies, we found that these methods identified over 98% of deaths in the cohorts [31]. Data on tumor subtype (any glioma versus glioblastoma [GBM]) was extracted directly from medical records for all cases.

## Statistical analyses

We began follow-up at the date of return of the initial questionnaire to inquire about anti-cholesterol medications (1990 in HPFS, 1994 in NHS, and 1999 in NHSII) and continued to the date of glioma diagnosis, death from another cause, or the end of follow-up (December 31, 2013 for NHS and NHSII; December 31, 2016 for HPFS), whichever came first. We excluded participants who reported a glioma diagnosis prior to return of the baseline questionnaire, but did not exclude patients with baseline cardiovascular disease or cancers other than glioma. After exclusions, we were left with 114,419 participants in NHS, 115,813 in NHSII and 50,223 in HPFS at baseline. We computed Cox proportional hazards models to generate age-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs), using months as the time metameter and age and calendar year as stratification variables for each statin exposure variable and each cardiovascular risk factor (i.e., hyperlipidemia, hypertension, diabetes, smoking status, and BMI). Tests of linear trend in glioma risk for increasing duration of statin use were assessed by assigning the median duration of statin use for each category, and treating those as a single continuous variable in Cox models. To address reverse causation, because pre-clinical tumor may cause changes in statin use, we applied follow-up data from 4 years prior to the current period in separate lagged analyses, resulting in exclusion of the first 4 years of follow-up for these calculations. Analyses of the female NHS and NHSII cohorts were combined by meta-analysis using the fixed-effect model due to the small number of cases (n = 84) in the NHSII cohort and to estimate HRs for women. 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.

## Results

### Cases and cohort characteristics

Across 4,430,700 person-years of follow-up, 483 cases of glioma were diagnosed (208 in NHS, 84 in NHSII, 191 in HPFS), of which 322 were GBM (Table 1). The majority of gliomas were astrocytomas (381 total, 79%), followed by oligodendroglioma (14 total, 3%) and mixed glioma (13 total, 3%). As expected, cases were generally older than the overall cohort.

### Associations with statin use

Ever statin use, compared to never use, was associated with a borderline increased risk of glioma in the combined cohorts (HR = 1.23, 95% CI 0.99–1.54) in age-adjusted analyses, but the findings were not statistically significant in women or in men separately (Table 2). For GBM, this association was similar in the combined cohorts (HR = 1.30, 95% CI 0.99–1.69), and was statistically significant among men (HR = 1.58, 95% CI 1.06–2.34), but not among women (HR = 1.10, 95% CI 0.77–1.58, Table 3). These results were similar in 4-year lagged analyses, with a significant increase in risk in the combined cohorts (HR = 1.34, 95% CI 1.03–1.73 comparing ever users to never users) and in women (HR = 1.53, 95% CI 1.09–2.14), but not among men (HR = 1.10, 95% CI 0.73–1.66, Table 4). After adjustment for cardiovascular risk factors, associations between ever statin use and glioma were strengthened, particularly in men. For glioma overall, the multivariable HR in combined cohorts was 1.43 (95% CI 1.10–1.86). Findings were similarly strengthened for GBM (multivariable HR = 1.51, 95% CI 1.10–2.07). The association between ever statin use and glioma using a 4-year lag were not substantially changed after adjustment (multivariable HR = 1.35, 95% CI 1.00–1.82), however.

For current statin use, overall results were similar to ever statin use. We observed slight non-significant increases in glioma risk compared with never users in age-adjusted analyses: HR = 1.22, 95% CI 0.97–1.55 in combined cohorts, HR = 1.18, 95% CI 0.87–1.61 for women, HR = 1.28, 95% CI 0.89–1.85 for men (Table 2). Age-adjusted results in the combined cohorts were similar for GBM (HR = 1.28, 95% CI 0.96–1.71, Table 3), and in 4-year lagged analyses (HR = 1.31, 95% CI 0.99–1.73, Table 4). Similar to the analysis for ever statin use, after adjustment for cardiovascular risk factors in multivariable models, the associations between current statin use and glioma were strengthened: for glioma overall, the multivariable HR for current versus never use was 1.42 (95% CI 1.08–1.88) and the corresponding multivariable HR for GBM was also increased (HR = 1.50, 95% CI 1.07–2.10).

Past statin use compared to never use was also significantly associated with increased risk in multivariable-adjusted analyses (HR = 1.51, 95% CI 1.01–2.26 for glioma, HR = 1.64, 95% CI 1.01–2.66 for GBM in combined cohorts). Findings for the multivariable-adjusted lagged

analyses were not materially different (HR in the combined cohorts = 1.51, 95% CI 0.90–2.53).

### Statin use duration

In age-adjusted models, longer duration of statin use was associated with increased risk of glioma in the combined cohorts (HR = 1.48, 95% CI 1.08–1.82 comparing > 8 years of use to never use, p-trend = 0.01). These findings for glioma overall were statistically significant among women (p-trend = 0.01) but not men (p-trend = 0.60). A similar pattern was observed for GBM only (p-trend = 0.03 in the combined cohorts). The results persisted after a 4 year lag (HR = 1.66, 95% CI 1.09–2.52 comparing > 8 years of use to never use in the combined cohorts, p-trend = 0.02).

Associations between statin use duration and glioma were also strengthened when adjusted for cardiovascular risk factors. Compared to those who had never used statins, in multivariable-adjusted models, those who used statins for > 8 years had increased risk for both glioma overall (HR = 1.72, 95% CI 1.21–2.45, p-trend = 0.003) and GBM (HR = 1.87, 95% CI 1.21–2.91, p-trend = 0.01). Similar associations were also observed in lagged analyses of glioma (HR = 1.64, 95% CI 1.05–2.57, p-trend = 0.04).

### Associations with cardiovascular disease risk factors

Diabetes, smoking, and BMI were not associated with glioma risk in age or multivariable-adjusted models. Hypertension was associated with increased risk of glioma in women (age-adjusted HR = 1.30, 95% CI 1.01–1.66) but not in men (HR = 0.99, 95% CI 0.73–1.35). For women, this finding persisted after multivariable adjustment for other cardiovascular risk factors. Results were similar for GBM and in 4-year lagged analyses for glioma. Although hyperlipidemia was not associated with glioma risk in age-adjusted models, in multivariable-adjusted models, including adjustment for statin use, hyperlipidemia was significantly inversely associated with glioma overall in the combined cohorts (HR = 0.74, 95% CI 0.59–0.93) and was borderline inversely associated with GBM (HR = 0.76, 95% CI 0.57–1.02). For overall glioma, in analyses of hyperlipidemia restricted to non-users of statins, we found a similar inverse relation (HR = 0.79, 95% CI 0.62–1.01). These findings for hyperlipidemia and glioma overall were substantially attenuated in the 4-year lagged analysis (for glioma overall, multivariable HR = 0.96, 95% CI 0.75–1.25).

### Associations by statin type

In total, 203 cases of glioma were diagnosed after statin type was initially recorded (Table 5). In the combined cohorts, hydrophilic statin use was associated with glioma risk in both age-adjusted (HR = 1.80, 95% CI 1.07–3.01) and multivariable-adjusted models (HR = 1.81, 95% CI 1.00–3.25), but lipophilic statin use was not (age-adjusted HR = 1.26, 95% CI 0.87–1.82; multivariable-adjusted HR = 1.33, 95% CI 0.86–2.07).

### Sensitivity analysis

As a sensitivity analysis of our categorization of all anti-cholesterol medications reported from 1990 onward as statins, we performed an analysis for ever statin use, starting from the time of direct assessment of statin type (2004 in NHS and HPFS, 2005 in NHSII, Table 5).

The results were similar in magnitude to the overall analysis in both univariable (HR = 1.32, 95% CI 0.97–1.79 comparing ever to never use) and multivariable analyses (HR = 1.38, 95% CI 0.94–2.02), but were not statistically significant due to the smaller number of cases (n = 203). In addition, we performed a similar analysis that followed subjects from the earlier first direct assessment of statin use in each cohort (2000 in NHS and HPFS, 2001 in NHSII). The results were again similar to the sensitivity analysis presented in Table 5 for both univariable (HR = 1.35, 95% CI 1.04–1.73 comparing ever to never use) and multivariable analyses (HR = 1.28, 95% CI 0.91–1.80).

## Discussion

This study, to the best of our knowledge, is the first prospective cohort investigation of the association between statin use and glioma risk. In contrast to our initial hypothesis of an inverse relation, our findings are consistent with the possibility of an increased risk of glioma associated with statin use. Findings were similar when restricted to GBM and were more prominent with longer duration use. Results were similar in 4-year lagged analyses for glioma, ruling out effects of reverse causation bias on the results. All associations were strengthened after adjustment for known cardiovascular risk factors. This study also demonstrated an unexpected significant inverse association between hyperlipidemia and glioma risk that was largely confined to the first 4 years of follow-up.

Statin use and subsequent risk of glioma has been investigated in three prior epidemiological studies: two case–control studies [21, 22] and one pharmacy linkage case–control study [20]. The first study, published in 2012, compared cases to controls regarding statin use at least twice weekly for longer than 6 months versus less frequent or never use, and reported a point estimate of 0.72 (95% CI 0.52–1.00). Two later studies reported very similar point estimates (0.76 comparing long-term users to never users [20], and 0.75 comparing those with ≥ 90 statin prescriptions versus no prior use [22, 32]). Additionally, two of these studies reported that longer duration of use may be associated with further reductions in risk of incident glioma, suggesting a duration-response relationship [20, 21]. A commentary published in response to these three papers performed a meta-analysis of the three results, suggesting a summary odds ratio of 0.75 (95% CI 0.62–0.90, $p = 0.0016$) [32].

One additional study of this association was based on a pooled analysis of randomized cardioprevention trials of statins in which randomized patients were followed prospectively for cancer outcomes. That study reported a null relationship between statin use and the more broad category of neurological cancers after a treatment period of 5 years ($p = 0.44$) [33]. However, as the analysis was based on only 124 cases (67 incident cases in the statin/high statin dose group versus 57 in the control/low statin dose group), the number of cases and limited follow-up period of 5 years may have been insufficient to observe an inverse or positive effect. It is also possible that indications for use in our prospective observational cohort may have differed from the recruitment protocols used in each of the 22 pooled trials.

Our data, on the other hand, suggest the possibility of an increased risk of glioma with statin use. The association was more pronounced after adjustment for cardiovascular risk factors that may be indications for statin use, including hyperlipidemia, and appeared to be more

prominent for hydrophilic as compared to lipophilic statins. Although the multivariable-adjusted results presented here are substantially different from those reported in the prior case–control studies, the age-adjusted results are more similar. Nevertheless, even the age-adjusted results suggest a positive association that has not been previously observed. Notably, none of the prior studies of statin use and glioma adjusted for hyperlipidemia or serum cholesterol [21]. One study adjusted for age, race, sex, and NSAID use [21], one adjusted for years of schooling, diabetes, stroke, and use of aspirin, COX-2 inhibitors, and other NSAIDs [20], and one matched on age, sex, practice of recruitment, and number of years under follow up, with additional adjustment for ethnicity, BMI, smoking, diabetes, and congestive heart failure [22]. Without adjustment for hyperlipidemia, prior estimates of the effect of statin use on glioma risk may have been downwardly biased by the potential confounding effect of hyperlipidemia that we observed in this study. Additionally, each of the prior studies used a retrospective analysis strategy that did not permit lagged analyses [20–22]. Although case–control studies are generally at greater risk of recall bias, two of the three prior studies used prescription records rather than questionnaires to identify statin users, eliminating the risk of recall bias [20, 22]. Of note, the pooled analysis of prospective cardioprevention trials all based on homogeneous populations of hyperlipidemic subjects (and thus not likely to be confounded by CVD risk factors) did not support an inverse association of statin use, similar to the present results.

One possible explanation for the inverse association we observed between hyperlipidemia and glioma is reverse causation. That is, if a preclinical glioma reduces circulating cholesterol levels by altering cholesterol metabolism, we would expect hyperlipidemia to be inversely associated with glioma risk due to a direct effect of the prediagnostic tumor. In our 4-year lagged analysis, the inverse association between hyperlipidemia and glioma risk that was observed in the overall analysis was substantially attenuated (for pooled cohorts, HR = 0.96, 95% CI 0.75–1.25 comparing those with hyperlipidemia to those without in the lagged analysis vs. HR = 0.74, 95% CI 0.59–0.93 in the overall analysis). Hence, reverse causation may be the most likely explanation for these findings, with results suggesting that a lagged period of approximately 4 years may be sufficient to produce an unbiased estimate of the effect of statin use on glioma risk. Present findings suggest that the inverse association between statin use and glioma risk in previous studies may have reflected confounding by indication for statin use (i.e., hyperlipidemia), a possibility that should be investigated in future studies.

Possible associations between circulating cholesterol levels and glioma risk have not been recently explored, but two case control [34, 35] and three cohort studies [36–38] from the late 1980s and early 1990s examined possible associations between cholesterol levels and brain tumor risk. Several of these studies included all brain malignancies without restriction to glioma, and both case–control studies may have been biased by suboptimal hospital-based control selection. The results of both case–control studies and one of the cohort studies suggested increased risk of brain cancer with higher serum cholesterol [34–36], while the other two cohort studies [37, 38], carried out in larger populations, showed no association between serum cholesterol and malignant brain tumor risk. None of the cohort studies considered potential for the time-dependency of associations between cholesterol and brain tumor risk that were demonstrated in the present study. Laboratory evidence suggests that

cholesterol may play an important role in brain tumor metabolism [39, 40]. Although the brain contains approximately 20% of total body cholesterol, almost none of this cholesterol comes from the peripheral supply. Instead, it is synthesized de novo by astrocytes, which generate cholesterol from glucose, glutamine, or acetyl-CoA [39]. Further studies on these associations should be carried out, with particular attention paid to timing of cholesterol measurement with respect to later glioma diagnosis.

Limitations of our data include a lack of important information on statin use, including exact indications, dose, and frequency. It is possible that dose, for example, may vary across populations, such as in men versus women. However, we could not evaluate statin dose, and statin use could not be validated by in-person interview or pharmacy review. In particular, for the earliest portion of follow up, statin use was not assessed directly. Instead, we considered exposure to any cholesterol-lowering medication after 1990 as statin exposure. From 1990 to 2000, statins constituted the majority of cholesterol-lowering medications used in the US, given their efficacy and minimal side effects compared to prior cholesterol-lowering therapies. Lemaitre et al. reported that use of statins increased four-fold from 1989 to 1996, from 1.9% of a sample of US adults in 1989 to 7.5% in 1996, dwarfing the prevalence of drugs from other classes like fibric acid derivatives and bile acid sequestrants, each of which were used by < 2% of the sample by 1996 [3]. In a separate study of cholesterol-lowering prescriptions from US retail pharmacies across the 1990s, the prevalence of statins rose rapidly from 54% of all prescriptions of cholesterol-lowering medications in 1991 to greater than 80% in 1996 [41]. By 2000, a prior study demonstrated that > 90% of the cholesterol-lowering drugs in HPFS were statins [42]. To reduce potential misclassification in our exposure definition, we also performed a sensitivity analysis based on direct assessment of statin use, which showed similar results, thereby demonstrating that misclassification was unlikely to have substantially affected the results.

Strengths of this study include the prospective design and biannual updates of important exposure and covariate information. Although the cohorts are comprised exclusively of males or females, the studies are conducted, maintained and managed with identical procedures for questionnaire design and administration, data collection, cleaning, coding, and analysis, ensuring consistent results regardless of sex. Participants were all health professionals, minimizing the potential for misclassification of statin use and other covariates. Importantly, regular updates of statin use and all covariates allowed for lagged analyses to assess whether timing of exposure to statins or cardiovascular risk factors affected glioma risk, and to evaluate the potential for reverse causation. Furthermore, the long duration of follow-up and large number of participants allowed us to analyze a relatively large number of glioma cases.

## Conclusion

In contrast to previously published case–control studies that reported inverse associations, in this prospective cohort investigation we found null or borderline positive associations between statin use and glioma risk with evidence of dose response for a longer duration of statin use. These findings were strengthened when adjusted for cardiovascular risk factors due to an unexpected inverse association between hyperlipidemia and glioma risk, and were

similar when restricted to GBM only and in 4-year lagged analyses. Considering the high prevalence of statin use, further studies on the role of statins and cholesterol in relation to glioma risk are warranted.

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**Table 1**

Age-adjusted demographics of study participants by cohort in 1994 for NHS, 1999 for NHSII, and 1990 for HPFS

| | NHS (n = 114,419) | | NHSII (n = 115,813) | | HPFS (n = 50,223) | |
|---|---|---|---|---|---|---|
| | **Incident glioma cases (n = 208)** | **Overall cohort** | **Incident glioma cases (n = 84)** | **Overall cohort** | **Incident glioma cases (n = 191)** | **Overall cohort** |
| Age, years (mean ± SD) | 62.4 (6.7) | 60.7 (7.2) | 46.3 (4.7) | 44.7 (4.7) | 59.4 (8.9) | 58.4 (9.8) |
| BMI, kg/m$^2$ (mean ± SD) | 26.5 (3.9) | 26.5 (5.2) | 26.1 (2.6) | 26.6 (6.3) | 26.3 (3.0) | 25.7 (3.4) |
| *Smoking status (%)* | | | | | | |
| Never smoker | 46 | 43 | 66 | 64 | 46 | 45 |
| Former smoker | 45 | 40 | 26 | 25 | 41 | 40 |
| Current smoker | 9 | 13 | 6 | 9 | 6 | 8 |
| Unknown | 0 | 4 | 2 | 1 | 7 | 7 |
| Diagnosed hypertension (%) | 29 | 23 | 12 | 9 | 19 | 19 |
| Diagnosed hyperlipidemia (%) | 30 | 28 | 5 | 12 | 21 | 21 |
| Diagnosed diabetes (%) | 5 | 4 | 0 | 2 | 1 | 3 |
| Current statin users (%) | 7 | 7 | 2 | 3 | 3 | 3 |

All values apart from age are age-adjusted to the distribution of the cohort. The calendar years were the starting points for follow-up in these analyses

*BMI* body mass index; *HPFS* health professionals follow up study; *NHS* nurses' health study; *NHSII* nurses' health study II; *SD* standard deviation

**Table 2**

Age and multivariable-adjusted risk of glioma in NHS, NHSII, and HPFS by statin use and cardiovascular risk factors, using Cox proportional hazard modeling

| | Women (n = 292)[a] | | | Men (n = 191) | | | Total (n = 483)[b] | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Cases** | **Hazard ratio** | **95% CI** | **Cases** | **Hazard ratio** | **95% CI** | **Cases** | **Hazard ratio** | **95% CI** |
| *Ever statin use* | | | | | | | | | |
| Never | 211 | Ref. | | 133 | Ref. | | 344 | Ref. | |
| Ever | 81 | 1.24 | 0.93–1.65 | 58 | 1.22 | 0.87–1.73 | 139 | 1.23 | 0.99–1.54 |
| *Ever statin use, multivariable-adjusted*[c] | | | | | | | | | |
| Never | 211 | Ref. | | 133 | Ref. | | 344 | Ref. | |
| Ever | 81 | 1.32 | 0.94–1.86 | 58 | 1.61 | 1.06–2.42 | 139 | 1.43 | 1.10–1.86 |
| *Current/past statin use* | | | | | | | | | |
| Never | 211 | Ref. | | 133 | Ref. | | 344 | Ref. | |
| Past | 22 | 1.54 | 0.96–2.46 | 11 | 1.02 | 0.53–1.94 | 33 | 1.33 | 0.91–1.95 |
| Current | 59 | 1.18 | 0.87–1.61 | 47 | 1.28 | 0.89–1.85 | 106 | 1.22 | 0.97–1.55 |
| *Current/past statin use, multivariable-adjusted*[c] | | | | | | | | | |
| Never | 211 | Ref. | | 133 | Ref. | | 344 | Ref. | |
| Past | 22 | 1.63 | 0.98–2.69 | 11 | 1.32 | 0.67–2.60 | 33 | 1.51 | 1.01–2.26 |
| Current | 59 | 1.26 | 0.88–1.81 | 47 | 1.69 | 1.10–2.60 | 106 | 1.42 | 1.08–1.88 |
| *Statin use duration* | | | | | | | | | |
| Never user | 211 | Ref. | | 133 | Ref. | | 344 | Ref. | |
| 0–4 years | 21 | 0.89 | 0.56–1.41 | 21 | 1.43 | 0.89–2.29 | 42 | 1.12 | 0.80–1.55 |
| > 4 years | 60 | 1.54 | 1.11–2.13 | 37 | 1.11 | 0.74–1.68 | 97 | 1.35 | 1.05–1.75 |
| P-trend | | | 0.01 | | | 0.61 | | | 0.02 |
| *Statin use duration, multivariable-adjusted*[c] | | | | | | | | | |
| Never user | 211 | Ref. | | 133 | Ref. | | 344 | Ref. | |
| 0–4 years | 21 | 0.95 | 0.58–1.55 | 21 | 1.81 | 1.08–3.03 | 42 | 1.29 | 0.90–1.85 |
| > 4 years | 60 | 1.65 | 1.13–2.42 | 37 | 1.47 | 0.92–2.37 | 97 | 1.58 | 1.17–2.13 |
| P-trend | | | 0.01 | | | 0.17 | | | 0.003 |
| *Statin use duration* | | | | | | | | | |

| | Women (n = 292)[a] | | | Men (n = 191) | | | Total (n = 483)[b] | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Cases** | **Hazard ratio** | **95% CI** | **Cases** | **Hazard ratio** | **95% CI** | **Cases** | **Hazard ratio** | **95% CI** |
| Never user | 211 | Ref. | | 133 | Ref. | | 344 | Ref. | |
| 0–4 years | 21 | 0.89 | 0.56–1.41 | 21 | 1.43 | 0.89–2.29 | 42 | 1.12 | 0.80–1.55 |
| 4–8 years | 24 | 1.41 | 0.91–2.18 | 12 | 1.05 | 0.57–1.93 | 36 | 1.27 | 0.89–1.82 |
| > 8 years | 36 | 1.79 | 1.18–2.71 | 25 | 1.15 | 0.71–1.86 | 61 | 1.48 | 1.08–2.03 |
| P-trend | | | 0.01 | | | 0.60 | | | 0.01 |
| *Statin use duration, multivariable-adjusted*[c] | | | | | | | | | |
| Never user | 211 | Ref. | | 133 | Ref. | | 344 | Ref. | |
| 0–4 years | 21 | 0.95 | 0.58–1.56 | 21 | 1.82 | 1.08–3.04 | 42 | 1.30 | 0.91–1.85 |
| 4–8 years | 24 | 1.55 | 0.96–2.49 | 12 | 1.37 | 0.71–2.63 | 36 | 1.48 | 1.01–2.18 |
| > 8 years | 36 | 1.86 | 1.17–2.97 | 25 | 1.54 | 0.90–2.65 | 61 | 1.72 | 1.21–2.45 |
| P-trend | | | 0.005 | | | 0.18 | | | 0.003 |
| *Hyperlipidemia* | | | | | | | | | |
| No | 156 | Ref. | | 110 | Ref. | | 266 | Ref. | |
| Yes | 136 | 0.95 | 0.74–1.22 | 81 | 0.79 | 0.58–1.06 | 217 | 0.88 | 0.73–1.07 |
| *Hyperlipidemia, multivariable-adjusted*[d] | | | | | | | | | |
| No | 156 | Ref. | | 110 | Ref. | | 266 | Ref. | |
| Yes | 136 | 0.80 | 0.59–1.09 | 81 | 0.66 | 0.46–0.95 | 217 | 0.74 | 0.59–0.93 |
| *Hyperlipidemia*[e] | | | | | | | | | |
| No | 153 | Ref. | | 98 | Ref. | | 251 | Ref. | |
| Yes | 58 | 0.81 | 0.60–1.11 | 35 | 0.76 | 0.51–1.13 | 93 | 0.79 | 0.62–1.01 |
| *Hyperlipidemia, multivariable-adjusted*[d,e] | | | | | | | | | |
| No | 153 | Ref. | | 98 | Ref. | | 251 | Ref. | |
| Yes | 58 | 0.78 | 0.57–1.08 | 35 | 0.79 | 0.53–1.18 | 93 | 0.78 | 0.61–1.01 |
| *Hypertension* | | | | | | | | | |
| No | 154 | Ref. | | 113 | Ref. | | 267 | Ref. | |
| Yes | 138 | 1.30 | 1.01–1.66 | 78 | 0.99 | 0.73–1.35 | 216 | 1.17 | 0.96–1.41 |
| *Hypertension, multivariable-adjusted*[f] | | | | | | | | | |
| No | 154 | Ref. | | 113 | Ref. | | 267 | Ref. | |

| | Women (n = 292)[a] | | | Men (n = 191) | | | Total (n = 483)[b] | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Cases** | **Hazard ratio** | **95% CI** | **Cases** | **Hazard ratio** | **95% CI** | **Cases** | **Hazard ratio** | **95% CI** |
| Yes | 138 | 1.36 | 1.04–1.78 | 78 | 1.04 | 0.75–1.43 | 216 | 1.21 | 0.99–1.49 |
| *Diabetes* | | | | | | | | | |
| No | 267 | Ref. | | 176 | Ref. | | 443 | Ref. | |
| Yes | 25 | 1.16 | 0.76–1.76 | 15 | 0.84 | 0.49–1.43 | 40 | 1.02 | 0.73–1.42 |
| *Diabetes, multivariable-adjusted*[g] | | | | | | | | | |
| No | 267 | Ref. | | 176 | Ref. | | 443 | Ref. | |
| Yes | 25 | 1.01 | 0.65–1.56 | 15 | 0.82 | 0.48–1.43 | 40 | 0.93 | 0.66–1.31 |
| *Smoking Status*[h] | | | | | | | | | |
| Never | 147 | Ref. | | 90 | Ref. | | 237 | Ref. | |
| Past | 123 | 1.06 | 0.83–1.36 | 84 | 0.93 | 0.69–1.26 | 207 | 1.01 | 0.83–1.22 |
| Current | 19 | 0.78 | 0.48–1.26 | 8 | 0.83 | 0.40–1.73 | 27 | 0.79 | 0.53–1.19 |
| *Smoking Status, multivariable-adjusted*[h, i] | | | | | | | | | |
| Never | 147 | Ref. | | 90 | Ref. | | 237 | Ref. | |
| Past | 123 | 1.06 | 0.83–1.35 | 84 | 0.93 | 0.68–1.25 | 207 | 1.00 | 0.83–1.21 |
| Current | 19 | 0.78 | 0.48–1.26 | 8 | 0.85 | 0.41–1.77 | 27 | 0.80 | 0.53–1.19 |
| *BMI*[h] | | | | | | | | | |
| < 25 kg/m$^2$ | 137 | Ref. | | 76 | Ref. | | 213 | Ref. | |
| 25–29.9 kg/m$^2$ | 79 | 0.86 | 0.65–1.14 | 79 | 1.02 | 0.74–1.41 | 158 | 0.92 | 0.75–1.15 |
| ≥ 30 kg/m$^2$ | 67 | 1.03 | 0.77–1.40 | 22 | 1.06 | 0.65–1.72 | 96 | 1.04 | 0.81–1.34 |
| *BMI, multivariable-adjusted*[h, j] | | | | | | | | | |
| < 25 kg/m$^2$ | 137 | Ref. | | 76 | Ref. | | 213 | Ref. | |
| 25–29.9 kg/m$^2$ | 79 | 0.82 | 0.61–1.10 | 79 | 1.03 | 0.74–1.42 | 158 | 0.91 | 0.73–1.12 |
| ≥ 30 kg/m$^2$ | 67 | 0.94 | 0.69–1.30 | 22 | 1.08 | 0.66–1.78 | 96 | 0.98 | 0.75–1.28 |

*BMI* body mass index, *HPFS* health professionals follow up study, *NHS* nurses' health study, *NHSII* nurses' health study II

[a] Obtained via meta-analysis of NHS and NHSII cohorts using the fixed effect model

[b] Obtained via meta-analysis of NHS, NHSII, and HPFS cohorts using the fixed effect model

[c] Adjusted for hypertension (yes vs. no), hyperlipidemia (yes vs. no), diabetes (yes vs. no), BMI (> 25 vs. 25–29.9 vs. > 30 vs. unknown kg/m$^2$), and smoking status (never vs. past vs. current vs. unknown)

[d] Adjusted for hypertension (yes vs. no), diabetes (yes vs. no), BMI (> 25 vs. 25–29.9 vs. > 30 vs. unknown kg/m$^2$), smoking status (never vs. past vs. current vs. unknown) and statin use duration (never vs. 0–4 years vs. 4–8 years vs. > 8 years)

[e] Restricted to never statin users

[f] Adjusted for hyperlipidemia (yes vs. no), diabetes (yes vs. no), BMI (> 25 vs. 25–29.9 vs. > 30 vs. unknown kg/m$^2$), smoking status (never vs. past vs. current vs. unknown), and statin use duration (never vs. 0–4 years vs. 4–8 years vs. > 8 years)

[g] Adjusted for hyperlipidemia (yes vs. no), hypertension (yes vs. no), smoking status (never vs. past vs. current vs. unknown), BMI (> 25 vs. 25–29.9 vs. > 30 vs. unknown kg/m$^2$), and statin use duration (never vs. 0–4 years vs. 4–8 years vs. > 8 years)

[h] Cases in these categories may not sum to the total number of cases due to missing values for some participants

[i] Adjusted for hyperlipidemia (yes vs. no), hypertension (yes vs. no), diabetes (yes vs. no), BMI (> 25 vs. 25–29.9 vs. > 30 vs. unknown kg/m$^2$), and statin use duration (never vs. 0–4 years vs. 4–8 years vs. > 8 years)

[j] Adjusted for hyperlipidemia (yes vs. no), hypertension (yes vs. no), diabetes (yes vs. no), smoking status (never vs. past vs. current vs. unknown), and statin use duration (never vs. 0–4 years vs. 4–8 years vs. > 8 years)

**Table 3**

Age and multivariable-adjusted risk of glioblastoma in NHS, NHSII, and HPFS by statin use and cardiovascular risk factors, using Cox proportional hazard modeling

| | Women (n = 182)[a] | | | Men (n = 140) | | | Total (n = 322)[b] | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Cases** | **Hazard ratio** | **95% CI** | **Cases** | **Hazard ratio** | **95% CI** | **Cases** | **Hazard ratio** | **95% CI** |
| *Ever statin use* | | | | | | | | | |
| Never | 134 | Ref. | | 91 | Ref. | | 225 | Ref. | |
| Ever | 48 | 1.10 | 0.77–1.58 | 49 | 1.58 | 1.06–2.34 | 97 | 1.30 | 0.99–1.69 |
| *Ever statin use, multivariable-adjusted*[c] | | | | | | | | | |
| Never | 134 | Ref. | | 91 | Ref. | | 225 | Ref. | |
| Ever | 48 | 1.11 | 0.72–1.69 | 49 | 2.26 | 1.40–3.66 | 97 | 1.51 | 1.10–2.07 |
| *Current/past statin use* | | | | | | | | | |
| Never | 134 | Ref. | | 91 | Ref. | | 225 | Ref. | |
| Past | 13 | 1.39 | 0.76–2.56 | 10 | 1.48 | 0.74–2.97 | 23 | 1.43 | 0.91–2.26 |
| Current | 35 | 1.05 | 0.70–1.55 | 39 | 1.60 | 1.06–2.43 | 74 | 1.28 | 0.96–1.71 |
| *Current/past statin use, multivariable-adjusted*[c] | | | | | | | | | |
| Never | 134 | Ref. | | 91 | Ref. | | 225 | Ref. | |
| Past | 13 | 1.37 | 0.72–2.61 | 10 | 2.07 | 0.99–4.36 | 23 | 1.64 | 1.01–2.66 |
| Current | 35 | 1.05 | 0.67–1.66 | 39 | 2.31 | 1.40–3.84 | 74 | 1.50 | 1.07–2.10 |
| *Statin use duration* | | | | | | | | | |
| Never user | 134 | Ref. | | 91 | Ref. | | 225 | Ref. | |
| 0–4 years | 10 | 1.05 | 0.68–1.64 | 19 | 1.90 | 1.14–3.16 | 29 | 1.23 | 0.82–1.84 |
| > 4 years | 38 | 1.23 | 0.75–2.00 | 30 | 1.38 | 0.86–2.22 | 60 | 1.43 | 1.05–1.96 |
| P-trend | | | 0.06 | | | 0.18 | | | 0.02 |
| *Statin use duration, multivariable-adjusted*[c] | | | | | | | | | |
| Never user | 134 | Ref. | | 91 | Ref. | | 225 | Ref. | |
| 0–4 years | 10 | 0.62 | 0.32–1.24 | 19 | 2.61 | 1.47–4.62 | 29 | 1.45 | 0.93–2.25 |
| > 4 years | 38 | 1.48 | 0.92–2.37 | 30 | 2.01 | 1.15–3.52 | 60 | 1.68 | 1.17–2.41 |
| P-trend | | | 0.06 | | | 0.04 | | | 0.005 |
| *Statin use duration* | | | | | | | | | |

| | Women (n = 182)[a] | | | Men (n = 140) | | | Total (n = 322)[b] | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Cases** | **Hazard ratio** | **95% CI** | **Cases** | **Hazard ratio** | **95% CI** | **Cases** | **Hazard ratio** | **95% CI** |
| Never user | 134 | Ref. | | 91 | Ref. | | 225 | Ref. | |
| 0–4 years | 10 | 0.61 | 0.32–1.17 | 19 | 1.90 | 1.14–3.17 | 29 | 1.23 | 0.82–1.84 |
| 4–8 years | 19 | 1.65 | 1.00–2.72 | 9 | 1.19 | 0.58–2.41 | 28 | 1.48 | 0.98–2.22 |
| > 8 years | 19 | 1.62 | 0.92–2.85 | 21 | 1.51 | 0.87–2.61 | 40 | 1.56 | 1.05–2.31 |
| P-trend | | | 0.10 | | | 0.17 | | | 0.03 |
| *Statin use duration, multivariable-adjusted*[c] | | | | | | | | | |
| Never user | 134 | Ref. | | 91 | Ref. | | 225 | Ref. | |
| 0–4 years | 10 | 0.62 | 0.32–1.24 | 19 | 2.62 | 1.48–4.65 | 29 | 1.45 | 0.93–2.25 |
| 4–8 years | 19 | 1.68 | 0.97–2.92 | 9 | 1.70 | 0.79–3.64 | 28 | 1.69 | 1.08–2.64 |
| > 8 years | 19 | 1.58 | 0.85–2.93 | 21 | 2.24 | 1.20–4.18 | 40 | 1.87 | 1.21–2.91 |
| P-trend | | | 0.12 | | | 0.04 | | | 0.01 |
| *Hyperlipidemia* | | | | | | | | | |
| No | 94 | Ref. | | 80 | Ref. | | 174 | Ref. | |
| Yes | 88 | 1.00 | 0.73–1.36 | 60 | 0.80 | 0.56–1.14 | 148 | 0.90 | 0.72–1.14 |
| *Hyperlipidemia, multivariable-adjusted*[d] | | | | | | | | | |
| No | 94 | Ref. | | 80 | Ref. | | 174 | Ref. | |
| Yes | 88 | 0.96 | 0.66–1.40 | 60 | 0.56 | 0.36–0.86 | 148 | 0.76 | 0.57–1.02 |
| *Hyperlipidemia*[e] | | | | | | | | | |
| No | 93 | Ref. | | 70 | Ref. | | 163 | Ref. | |
| Yes | 41 | 0.93 | 0.63–1.35 | 21 | 0.64 | 0.39–1.06 | 62 | 0.81 | 0.60–1.09 |
| *Hyperlipidemia, multivariable-adjusted*[d,e] | | | | | | | | | |
| No | 93 | Ref. | | 70 | Ref. | | 163 | Ref. | |
| Yes | 41 | 0.91 | 0.61–1.34 | 21 | 0.67 | 0.40–1.10 | 62 | 0.81 | 0.59–1.10 |
| *Hypertension* | | | | | | | | | |
| No | 100 | Ref. | | 80 | Ref. | | 180 | Ref. | |
| Yes | 82 | 1.12 | 0.82–1.53 | 60 | 1.12 | 0.78–1.59 | 142 | 1.12 | 0.88–1.41 |
| *Hypertension, multivariable-adjusted*[f] | | | | | | | | | |
| No | 100 | Ref. | | 80 | Ref. | | 180 | Ref. | |

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| | Women (n = 182)[a] | | | Men (n = 140) | | | Total (n = 322)[b] | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Cases** | **Hazard ratio** | **95% CI** | **Cases** | **Hazard ratio** | **95% CI** | **Cases** | **Hazard ratio** | **95% CI** |
| Yes | 82 | 1.15 | 0.82–1.62 | 60 | 1.16 | 0.80–1.69 | 142 | 1.15 | 0.90–1.49 |
| *Diabetes* | | | | | | | | | |
| No | 166 | Ref. | | 129 | Ref. | | 295 | Ref. | |
| Yes | 16 | 1.13 | 0.67–1.91 | 11 | 0.87 | 0.46–1.63 | 27 | 1.01 | 0.68–1.52 |
| *Diabetes, multivariable-adjusted*[g] | | | | | | | | | |
| No | 166 | Ref. | | 129 | Ref. | | 295 | Ref. | |
| Yes | 16 | 1.02 | 0.59–1.77 | 11 | 0.82 | 0.43–1.55 | 27 | 0.93 | 0.61–1.41 |
| *Smoking Status*[h] | | | | | | | | | |
| Never | 92 | Ref. | | 66 | Ref. | | 158 | Ref. | |
| Past | 76 | 1.03 | 0.75–1.41 | 64 | 0.95 | 0.67–1.35 | 140 | 0.99 | 0.79–1.25 |
| Current | 12 | 0.79 | 0.43–1.45 | 3 | 0.41 | 0.13–1.30 | 15 | 0.69 | 0.40–1.18 |
| *Smoking Status, multivariable-adjusted*[h, i] | | | | | | | | | |
| Never | 85 | Ref. | | 66 | Ref. | | 158 | Ref. | |
| Past | 76 | 1.02 | 0.75–1.40 | 64 | 0.94 | 0.66–1.33 | 140 | 0.99 | 0.78–1.24 |
| Current | 12 | 0.78 | 0.43–1.44 | 3 | 0.42 | 0.13–1.34 | 15 | 0.69 | 0.40–1.18 |
| *BMI*[h] | | | | | | | | | |
| < 25 kg/m$^2$ | 87 | Ref. | | 55 | Ref. | | 142 | Ref. | |
| 25–29.9 kg/m$^2$ | 47 | 0.78 | 0.54–1.12 | 57 | 0.98 | 0.67–1.44 | 104 | 0.87 | 0.67–1.13 |
| ≥ 30 kg/m$^2$ | 41 | 0.99 | 0.68–1.46 | 16 | 1.02 | 0.57–1.80 | 57 | 1.00 | 0.73–1.37 |
| *BMI, multivariable-adjusted*[h, j] | | | | | | | | | |
| < 25 kg/m$^2$ | 87 | Ref. | | 55 | Ref. | | 142 | Ref. | |
| 25–29.9 kg/m$^2$ | 47 | 0.76 | 0.52–1.10 | 57 | 0.96 | 0.66–1.41 | 104 | 0.85 | 0.65–1.11 |
| ≥ 30 kg/m$^2$ | 41 | 0.94 | 0.63–1.40 | 16 | 0.98 | 0.55–1.76 | 57 | 0.95 | 0.68–1.33 |

*BMI* body mass index, *HPFS* health professionals follow up study, *NHS* nurses' health study, *NHSII* nurses' health study II

[a] Obtained via meta-analysis of NHS and NHSII cohorts using the fixed effect model

[b] Obtained via meta-analysis of NHS, NHSII, and HPFS cohorts using the fixed effect model

[c] Adjusted for hypertension (yes vs. no), hyperlipidemia (yes vs. no), diabetes (yes vs. no), BMI (> 25 vs. 25–29.9 vs. > 30 vs. unknown kg/m$^2$), and smoking status (never vs. past vs. current vs. unknown)

[d] Adjusted for hypertension (yes vs. no), diabetes (yes vs. no), BMI (> 25 vs. 25–29.9 vs. > 30 vs. unknown kg/m$^2$), smoking status (never vs. past vs. current vs. unknown) and statin use duration (never vs. 0–4 years vs. 4–8 years vs. > 8 years)

[e] Restricted to never statin users

[f] Adjusted for hyperlipidemia (yes vs. no), diabetes (yes vs. no), BMI (> 25 vs. 25–29.9 vs. > 30 vs. unknown kg/m$^2$), smoking status (never vs. past vs. current vs. unknown), and statin use duration (never vs. 0–4 years vs. 4–8 years vs. > 8 years)

[g] Adjusted for hyperlipidemia (yes vs. no), hypertension (yes vs. no), smoking status (never vs. past vs. current vs. unknown), BMI (> 25 vs. 25–29.9 vs. > 30 vs. unknown kg/m$^2$), and statin use duration (never vs. 0–4 years vs. 4–8 years vs. > 8 years)

[h] Cases in these categories may not sum to the total number of cases due to missing values for some participants

[i] Adjusted for hyperlipidemia (yes vs. no), hypertension (yes vs. no), diabetes (yes vs. no), BMI (> 25 vs. 25–29.9 vs. > 30 vs. unknown kg/m$^2$), and statin use duration (never vs. 0–4 years vs. 4–8 years vs. > 8 years)

[j] Adjusted for hyperlipidemia (yes vs. no), hypertension (yes vs. no), diabetes (yes vs. no), smoking status (never vs. past vs. current vs. unknown), and statin use duration (never vs. 0–4 years vs. 4–8 years vs. > 8 years)

**Table 4**

Age and multivariable adjusted risk of glioma in NHS, NHSII, and HPFS by 4-year lagged statin use and cardiovascular risk factors, using Cox proportional hazard modeling

| | Women (n = 224)[a] | | | Men (n = 158) | | | Total (n = 382)[b] | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Cases** | **Hazard ratio** | **95% CI** | **Cases** | **Hazard ratio** | **95% CI** | **Cases** | **Hazard ratio** | **95% CI** |
| *Ever statin use* | | | | | | | | | |
| Never | 170 | Ref. | | 122 | Ref. | | 292 | Ref. | |
| Ever | 54 | 1.53 | 1.09–2.14 | 36 | 1.10 | 0.73–1.66 | 90 | 1.34 | 1.03–1.74 |
| *Ever statin use, multivariable-adjusted*[c] | | | | | | | | | |
| Never | 170 | Ref. | | 122 | Ref. | | 292 | Ref. | |
| Ever | 54 | 1.50 | 1.02–2.22 | 36 | 1.16 | 0.73–1.84 | 90 | 1.35 | 1.00–1.82 |
| *Current/past statin use* | | | | | | | | | |
| Never | 170 | Ref. | | 122 | Ref. | | 292 | Ref. | |
| Past | 11 | 1.78 | 0.94–3.37 | 7 | 1.17 | 0.53–2.56 | 18 | 1.50 | 0.92–2.47 |
| Current | 43 | 1.49 | 1.04–2.14 | 29 | 1.09 | 0.70–1.69 | 72 | 1.31 | 0.99–1.73 |
| *Current/past statin use, multivariable-adjusted*[c] | | | | | | | | | |
| Never | 170 | Ref. | | 122 | Ref. | | 292 | Ref. | |
| Past | 11 | 1.72 | 0.88–3.35 | 7 | 1.25 | 0.55–2.81 | 18 | 1.51 | 0.90–2.53 |
| Current | 43 | 1.46 | 0.97–2.20 | 29 | 1.14 | 0.70–1.86 | 72 | 1.32 | 0.96–1.81 |
| *Statin use duration* | | | | | | | | | |
| Never user | 170 | Ref. | | 122 | Ref. | | 292 | Ref. | |
| 0–4 years | 23 | 1.37 | 0.88–2.14 | 15 | 1.19 | 0.68–2.05 | 38 | 1.30 | 0.92–1.83 |
| >4 years | 31 | 1.77 | 1.14–2.73 | 21 | 1.04 | 0.63–1.73 | 52 | 1.41 | 1.02–1.97 |
| P-trend | | | 0.01 | | | 0.84 | | | 0.03 |
| *Statin use duration, multivariable-adjusted*[c] | | | | | | | | | |
| Never user | 170 | Ref. | | 122 | Ref. | | 292 | Ref. | |
| 0–4 years | 23 | 1.39 | 0.85–2.26 | 15 | 1.23 | 0.69–2.22 | 38 | 1.32 | 0.91–1.92 |
| > 4 years | 31 | 1.66 | 1.02–2.68 | 21 | 1.11 | 0.64–1.93 | 52 | 1.39 | 0.97–2.00 |
| P-trend | | | 0.04 | | | 0.75 | | | 0.07 |
| *Statin use duration* | | | | | | | | | |

| | Women (n = 224)[a] | | | Men (n = 158) | | | Total (n = 382)[b] | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Cases** | **Hazard ratio** | **95% CI** | **Cases** | **Hazard ratio** | **95% CI** | **Cases** | **Hazard ratio** | **95% CI** |
| Never user | 170 | Ref. | | 122 | Ref. | | 292 | Ref. | |
| 0–4 years | 23 | 1.37 | 0.88–2.14 | 15 | 1.19 | 0.69–2.07 | 38 | 1.30 | 0.92–1.84 |
| 4–8 years | 17 | 1.72 | 1.02–2.92 | 5 | 0.58 | 0.23–1.44 | 22 | 1.31 | 0.83–2.07 |
| > 8 years | 14 | 1.97 | 1.06–3.63 | 16 | 1.43 | 0.81–2.54 | 30 | 1.66 | 1.09–2.52 |
| P-trend | | | 0.01 | | | 0.42 | | | 0.02 |
| *Statin use duration, multivariable-adjusted*[c] | | | | | | | | | |
| Never user | 170 | Ref. | | 122 | Ref. | | 292 | Ref. | |
| 0–4 years | 23 | 1.39 | 0.85–2.26 | 15 | 1.24 | 0.69–2.24 | 38 | 1.33 | 0.91–1.93 |
| 4–8 years | 17 | 1.65 | 0.94–2.90 | 5 | 0.61 | 0.24–1.56 | 22 | 1.27 | 0.78–2.05 |
| > 8 years | 14 | 1.79 | 0.94–3.43 | 16 | 1.52 | 0.82–2.82 | 30 | 1.64 | 1.05–2.57 |
| P-trend | | | 0.05 | | | 0.33 | | | 0.04 |
| *Hyperlipidemia* | | | | | | | | | |
| No | 123 | Ref. | | 88 | Ref. | | 211 | Ref. | |
| Yes | 101 | 1.16 | 0.86–1.55 | 70 | 1.00 | 0.72–1.38 | 171 | 1.08 | 0.87–1.35 |
| *Hyperlipidemia, multivariable-adjusted*[d] | | | | | | | | | |
| No | 123 | Ref. | | 88 | Ref. | | 211 | Ref. | |
| Yes | 101 | 0.95 | 0.67–1.34 | 70 | 0.98 | 0.68–1.43 | 171 | 0.96 | 0.75–1.25 |
| *Hyperlipidemia*[e] | | | | | | | | | |
| No | 119 | Ref. | | 85 | Ref. | | 204 | Ref. | |
| Yes | 51 | 1.04 | 0.73–1.47 | 37 | 0.94 | 0.63–1.40 | 88 | 0.99 | 0.77–1.29 |
| *Hyperlipidemia, multivariable-adjusted*[d,e] | | | | | | | | | |
| No | 119 | Ref. | | 85 | Ref. | | 204 | Ref. | |
| Yes | 51 | 0.98 | 0.68–1.40 | 37 | 0.98 | 0.65–1.46 | 88 | 0.98 | 0.75–1.28 |
| *Hypertension* | | | | | | | | | |
| No | 129 | Ref. | | 104 | Ref. | | 233 | Ref. | |
| Yes | 95 | 1.36 | 1.02–1.80 | 54 | 0.90 | 0.64–1.27 | 149 | 1.15 | 0.92–1.43 |
| *Hypertension, multivariable-adjusted*[f] | | | | | | | | | |
| No | 129 | Ref. | | 104 | Ref. | | 233 | Ref. | |

| | Women (n = 224)[a] | | | Men (n = 158) | | | Total (n = 382)[b] | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Cases** | **Hazard ratio** | **95% CI** | **Cases** | **Hazard ratio** | **95% CI** | **Cases** | **Hazard ratio** | **95% CI** |
| Yes | 95 | 1.34 | 0.99–1.82 | 54 | 0.89 | 0.62–1.28 | 149 | 1.13 | 0.90–1.43 |
| *Diabetes* | | | | | | | | | |
| No | 162 | Ref. | | 149 | Ref. | | 357 | Ref. | |
| Yes | 16 | 1.34 | 0.79–2.26 | 9 | 0.74 | 0.37–1.47 | 25 | 1.08 | 0.71–1.63 |
| *Diabetes, multivariable-adjusted*[g] | | | | | | | | | |
| No | 162 | Ref. | | 149 | Ref. | | 357 | Ref. | |
| Yes | 16 | 1.15 | 0.67–1.99 | 9 | 0.73 | 0.36–1.47 | 25 | 0.97 | 0.63–1.49 |
| Smoking Status[h] | | | | | | | | | |
| Never | 114 | Ref. | | 81 | Ref. | | 190 | Ref. | |
| Past | 94 | 1.08 | 0.82–1.43 | 67 | 0.85 | 0.61–1.18 | 160 | 0.98 | 0.79–1.21 |
| Current | 15 | 0.75 | 0.43–1.28 | 6 | 0.65 | 0.28–1.50 | 18 | 0.72 | 0.46–1.13 |
| *Smoking Status, multivariable-adjusted*[h, i] | | | | | | | | | |
| Never | 114 | Ref. | | 81 | Ref. | | 190 | Ref. | |
| Past | 94 | 1.06 | 0.80–1.41 | 67 | 0.85 | 0.61–1.18 | 160 | 0.97 | 0.78–1.20 |
| Current | 15 | 0.74 | 0.43–1.27 | 6 | 0.66 | 0.29–1.53 | 18 | 0.72 | 0.45–1.13 |
| *BMI*[h] | | | | | | | | | |
| < 25 kg/m$^2$ | 108 | Ref. | | 65 | Ref. | | 162 | Ref. | |
| 25–29.9 kg/m$^2$ | 58 | 0.76 | 0.55–1.06 | 61 | 0.90 | 0.63–1.28 | 121 | 0.82 | 0.65–1.05 |
| ≥ 30 kg/m$^2$ | 53 | 1.00 | 0.71–1.40 | 22 | 1.20 | 0.73–1.96 | 74 | 1.06 | 0.80–1.40 |
| *BMI, multivariable-adjusted*[h, j] | | | | | | | | | |
| < 25 kg/m$^2$ | 108 | Ref. | | 65 | Ref. | | 162 | Ref. | |
| 25–29.9 kg/m$^2$ | 58 | 0.71 | 0.51–0.99 | 61 | 0.92 | 0.64–1.31 | 121 | 0.80 | 0.63–1.02 |
| ≥ 30 kg/m$^2$ | 53 | 0.89 | 0.63–1.28 | 22 | 1.28 | 0.77–2.13 | 74 | 1.00 | 0.75–1.34 |

*BMI* body mass index, *HPFS* health professionals follow up study, *NHS* nurses' health study, *NHSII* nurses' health study II

[a] Obtained via meta-analysis of NHS and NHSII cohorts using the fixed effect model

[b] Obtained via meta-analysis of NHS, NHSII, and HPFS cohorts using the fixed effect model

[c] Adjusted for hypertension (yes vs. no), hyperlipidemia (yes vs. no), diabetes (yes vs. no), BMI (> 25 vs. 25–29.9 vs. > 30 vs. unknown kg/m$^2$), and smoking status (never vs. past vs. current vs. unknown)

[d] Adjusted for hypertension (yes vs. no), diabetes (yes vs. no), BMI (> 25 vs. 25–29.9 vs. > 30 vs. unknown kg/m$^2$), smoking status (never vs. past vs. current vs. unknown) and statin use duration (never vs. 0–4 years vs. 4–8 years vs. > 8 years)

[e] Restricted to never statin users

[f] Adjusted for hyperlipidemia (yes vs. no), diabetes (yes vs. no), BMI (> 25 vs. 25–29.9 vs. > 30 vs. unknown kg/m$^2$), smoking status (never vs. past vs. current vs. unknown), and statin use duration (never vs. 0–4 years vs. 4–8 years vs. > 8 years)

[g] Adjusted for hyperlipidemia (yes vs. no), hypertension (yes vs. no), smoking status (never vs. past vs. current vs. unknown), BMI (> 25 vs. 25–29.9 vs. > 30 vs. unknown kg/m$^2$), and statin use duration (never vs. 0–4 years vs. 4–8 years vs. > 8 years)

[h] Cases in these categories may not sum to the total number of cases due to missing values for some participants

[i] Adjusted for hyperlipidemia (yes vs. no), hypertension (yes vs. no), diabetes (yes vs. no), BMI (> 25 vs. 25–29.9 vs. > 30 vs. unknown kg/m$^2$), and statin use duration (never vs. 0–4 years vs. 4–8 years vs. > 8 years)

[j] Adjusted for hyperlipidemia (yes vs. no), hypertension (yes vs. no), diabetes (yes vs. no), smoking status (never vs. past vs. current vs. unknown), and statin use duration (never vs. 0–4 years vs. 4–8 years vs. > 8 years)

**Table 5**

Age and multivariable-adjusted risk of glioma in NHS, NHSII, and HPFS by type of statin use, using Cox proportional hazard modeling

| | Women (n = 131)[a] | | | Men (n = 72) | | | Total (n = 203)[b] | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Cases** | **Hazard ratio** | **95% CI** | **Cases** | **Hazard ratio** | **95% CI** | **Cases** | **Hazard ratio** | **95% CI** |
| *Hydrophilic statin use*[c,d] | | | | | | | | | |
| Never | 78 | Ref. | | 34 | Ref. | | 112 | Ref. | |
| Ever | 12 | 1.54 | 0.79–3.03 | 8 | 2.22 | 0.99–4.98 | 20 | 1.80 | 1.07–3.01 |
| *Hydrophilic statin use*[c,d,e] | | | | | | | | | |
| Never | 78 | Ref. | | 34 | Ref. | | 112 | Ref. | |
| Ever | 12 | 1.52 | 0.70–3.30 | 8 | 2.28 | 0.93–5.63 | 20 | 1.81 | 1.00–3.25 |
| *Lipophilic statin use*[c,f] | | | | | | | | | |
| Never | 78 | Ref. | | 34 | Ref. | | 112 | Ref. | |
| Ever | 23 | 1.25 | 0.75–2.07 | 23 | 1.27 | 0.74–2.18 | 46 | 1.26 | 0.87–1.82 |
| *Lipophilic statin use*[c,e,f] | | | | | | | | | |
| Never | 78 | Ref. | | 34 | Ref. | | 112 | Ref. | |
| Ever | 23 | 1.32 | 0.73–2.39 | 23 | 1.34 | 0.70–2.58 | 46 | 1.33 | 0.86–2.07 |
| *Ever statin use* | | | | | | | | | |
| Never | 78 | Ref. | | 34 | Ref. | | 112 | Ref. | |
| Ever | 53 | 1.41 | 0.94–2.10 | 38 | 1.21 | 0.75–1.93 | 91 | 1.32 | 0.97–1.79 |
| *Ever statin use*[e] | | | | | | | | | |
| Never | 78 | Ref. | | 34 | Ref. | | 112 | Ref. | |
| Ever | 53 | 1.43 | 0.86–2.36 | 38 | 1.31 | 0.74–2.35 | 91 | 1.38 | 0.94–2.02 |

*HPFS* health professionals follow up study, *NHS* nurses' health study, *NHSII* nurses' health study II

[a] Obtained via meta-analysis of NHS and NHSII cohorts using the fixed effect model

[b] Obtained via meta-analysis of NHS, NHSII, and HPFS cohorts using the fixed effect model

[c] Totals for specific statin types may not sum to total case counts due to exclusion of all participants who did not specify statin brand

[d] Hydrophilic statins were considered Crestor® (rosuvastatin) and Pravachol® (pravastatin)

[e] Adjusted for hypertension (yes vs. no), hyperlipidemia (yes vs. no), diabetes (yes vs. no), body mass index (> 25 vs. 25–29.9 vs. > 30 vs. unknown kg/m$^2$), and smoking status (never vs. past vs. current vs. unknown)

[f] Lipophilic statins were considered Mevacor® (lovastatin), Zocor® (simvastatin), and Lipitor® (atorvastatin)



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