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Circulating lipids and glioma risk: results from the UK Biobank, Nurses' Health Study, and Health Professionals Follow-Up Study

David J. Cote, PhD[1,2,*], **Stephanie A. Smith-Warner, PhD**[3,4,*], **Jordan H. Creed, MS**[5], **Jeremy Furtado, ScD**[4], **Travis Gerke, ScD**[5], **Molin Wang, PhD**[1,3], **Youngchul Kim, PhD**[5], **Meir J. Stampfer, MD, DrPH**[1,3,4], **Kathleen M. Egan, ScD**[5]

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

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

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

Abstract

Purpose: Evidence is mixed on whether cholesterol plays a role in the pathogenesis of glioma. We explored the associations between circulating lipids and glioma risk in three prospective cohorts.

Methods: Using prospective data from the UK Biobank, we examined the associations of total cholesterol (TC), high- and low-density lipoprotein cholesterol (HDL-C, LDL-C), and triglycerides (TG) with glioma risk in multivariable (MV)-adjusted Cox proportional hazards models. Within the Nurses' Health Study (NHS) and the Health Professionals Follow-Up Study (HPFS), we carried out a matched, nested case-control study to examine these same associations.

Results: In the UK Biobank, 490 gliomas accrued over 2,358,964 person-years. TC was not significantly associated with glioma risk (MV HR=1.20, 95%CI: 0.89-1.61 for highest quartile vs. lowest, p-trend=0.24). In four-year lagged analyses (n=229), higher TC was associated with significantly higher risk of glioma in men (MV HR=2.26, 95%CI: 1.32-3.89, p-trend=0.002) but not women (MV HR =1.28, 95%CI: 0.61-2.68, p-trend=0.72); similar findings emerged for HDL-C and, to a lesser extent, LDL-C. In the NHS/HPFS, no significant associations were found between cholesterol and glioma risk. No significant associations were identified for TG.

Conclusion: In the UK Biobank, higher prediagnostic TC and HDL-C levels were associated with higher risk of glioma in four-year lagged analyses, but not in non-lagged analyses, in men

Corresponding Author: David J. Cote, PhD, Channing Division of Network Medicine, Brigham and Women's Hospital, 181 Longwood Avenue, Boston, MA 02115, Phone: (617) 525-2749 Fax: (617) 525-2008, david_cote@hms.harvard.edu.
*Authors contributed equally

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only. These findings merit further investigation, given that there are few risk factors and no reliable biomarkers of risk identified for glioma.

Keywords

glioma; risk; epidemiology; cholesterol; cohort; UK Biobank

Introduction

Glioma, the most common primary brain malignancy, has few known risk factors (1). Recent evidence from both epidemiologic and basic research is mixed on whether cholesterol plays a role in the pathogenesis and progression of these tumors (2).

Several studies in the late 1980s and early 1990s examined possible associations between serum cholesterol and brain tumor risk, with three studies suggesting increased risk with higher serum cholesterol (3–5) and two showing no association (6, 7). These studies were small (n=32-150 cases) and combined multiple tumor types (e.g., glioma and meningioma) that have been shown to have different risk factors; few considered cholesterol fractions. Recently, we reported in the Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS) that self-reported hyperlipidemia was inversely associated with glioma risk, but only in the four years immediately preceding diagnosis (2). This suggested that pre-clinical glioma may have a cholesterol lowering effect prior to diagnosis, as opposed to serum cholesterol levels playing a causal role in the etiology of glioma. Most recently, a large Mendelian randomization analysis demonstrated no association between genetically-determined cholesterol and glioma risk (8).

As the association between direct measurements of cholesterol and glioma risk has not been explored prospectively, we carried out two parallel analyses. Using data from the UK Biobank, we investigated the association between blood circulating lipid levels and glioma incidence in a prospective cohort study, using lagged analyses to reduce the possibility of reverse causation. Separately, using data from the NHS and HPFS, we carried out a matched, nested case-control study examining the association between prediagnostic circulating cholesterol and glioma incidence.

Methods

UK Biobank Analysis

Study Design and Participants—The UK Biobank is a prospective, population-based cohort study, established in the United Kingdom in 2006-2010 with enrollment of approximately 500,000 volunteers aged 40 to 69 (9, 10). Participants were identified from National Health Service patient registries, and completed automated questionnaires that included questions about demographic features, medical history, medication use, lifestyle factors, and diet. Additionally, all cohort members provided blood samples at baseline. All participants of the UK Biobank provided written consent at recruitment.

Outcome Ascertainment—Cancer incidence in the UK Biobank is tracked by linkage to the UK's National Health Service Central Registers, which allows for identification of

patients diagnosed with cancer. We included all patients diagnosed from 2006 to 2016 with incident intracranial glioma (ICD9/10: 191 and C71), subtyped as glioblastoma (GBM, 9440-9441) or non-GBM (982, 9400-01, 9420, 9424-25, 9450-9451) (11).

Cholesterol and Triglyceride Assessment—Blood samples were collected at baseline from UK Biobank participants using the vacutainer system, and were transported overnight by commercial courier to a central laboratory, where they were processed and stored as aliquots at ultra-low temperature (12). Cholesterol levels measured in all baseline blood samples by UK Biobank investigators included direct measurement of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG). Assays for TC and the three cholesterol fractions were manufactured by Beckman Coulter, Ltd. (Brea, California, United States), and each was conducted on the Beckman Coulter AU5800 analytical platform. For TC and TG, the assays were enzymatic, for HDL-C, the assay used enzyme immune-inhibition, and for LDL-C, the assay used enzymatic selective protection. The analytical range for TC was 1-5 mmol/L, for HDL-C was 0.05-4.65 mmol/L, for LDL-C was 0.26-10.3 mmol/L, and for TG was 0.1-11.3 mmol/L (13). The UK Biobank computed coefficients of variation (CV) for each assay among high, medium, and low concentration samples demonstrated excellent performance (for medium level, 1.65% for TC, 1.76% for HDL-C, 1.59% for LDL-C, and 2.18% for TG).

Statin Use Assessment—Prior to the baseline visit, UK Biobank participants were provided with a pre-visit questionnaire, which aimed to improve recall of information that they may not be able to recall immediately at their visit. At the baseline visit, UK Biobank participants were then asked during a verbal interview to report all current medications. We categorized statin use as current use of any statin medication at baseline versus no use at baseline.

Covariate Assessment—At the baseline visit, participants completed a touchscreen questionnaire that included detailed questions on sociodemographic and lifestyle characteristics, family and medical history, and psychosocial factors. Missing data occurred when a participant completed the baseline questionnaire but did not select a response for a particular question. The overall proportion of missing data for covariates was low (<1.8% for each).

Statistical Analyses—To assess the associations between lipid levels and glioma risk, we constructed multivariable-adjusted Cox proportional hazards models using quartiles of each measure of circulating cholesterol using the distribution of levels among participants in the UK Biobank with that measure. Participants with missing data for the primary exposure being evaluated were excluded from that analysis. Follow-up began at enrollment, and continued until diagnosis of glioma or another cancer, death, or last linkage, whichever occurred first. In multivariable analyses, the covariates included age (continuous), sex, race (White vs. non-White), history of diabetes (yes vs. no), history of hypertension (yes vs. no), statin use (current use at baseline vs. no current use), BMI (<25 kg/m^2 vs. 25-<30 kg/m^2 vs. ≥30 kg/m^2), and smoking status (never vs. past vs. current). Covariates were chosen to reduce the risk of confounding of the associations between lipid levels and glioma risk, and

to create a comparable analysis to our prior work on self-reported hypercholesterolemia and statin use in NHS/HPFS (2). Missing values for covariates were modeled with an indicator category. Tests of linear trend in glioma risk for higher levels of circulating lipids were assessed by assigning the median value of the lipid biomarker for each quartile, and treating those values as a single continuous variable in Cox models. Additionally, we performed a four-year lagged analysis, where we began follow-up from four years after enrollment, resulting in exclusion of the first four years of follow-up. The aim of this analysis was to exclude the preclinical period, thereby reducing the possibility that blood circulating lipid concentrations were markers of preclinical disease. In secondary analyses, we restricted the study population to non-users of statins at baseline, subgrouped by sex, and examined GBM and non-GBM separately. We also performed an analysis examining the overall association between current statin use at baseline and glioma risk.

Nurses' Health Study and Health Professionals Follow-Up Study Analysis

Study Design and Participants—The methods of the NHS and HPFS have been reported in previous publications (14–16). Briefly, 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. Participants in both cohorts completed a baseline questionnaire on lifestyle and medical factors. Subsequent follow-up questionnaires have been completed every two years to assess updated information. Follow-up rates in the cohorts have exceeded 90% (17). The study protocol was approved by the institutional review boards of the Harvard T.H. Chan School of Public Health and the Brigham and Women's Hospital, as well as those of participating cancer registries.

Blood samples were collected from 32,826 women in NHS from 1989 to 1990 and from 18,225 men in HPFS between 1993 and 1995, and were subsequently stored in freezers under specific protocols, as previously described (18–20). Among patients with available blood samples in NHS and HPFS, we conducted a nested case control analysis by matching glioma cases confirmed by medical record review with controls in a 1:2 ratio on age (+/− one year), cohort (which matches on sex), fasting status (fasting vs. non-fasting), month and year of sample collection (+/− one month), and ethnic background (White vs. non-White). We used risk set sampling, selecting controls from the population in the cohort alive and at risk of glioma at the time of each case occurrence.

Outcome Ascertainment—Primary brain malignancy cases were self-reported on questionnaires and then confirmed by medical record review, or determined by medical record review posthumously. Only cases with confirmed ICD-9-CM diagnoses of 191.x were included in this analysis. Data on tumor subtype (GBM and non-GBM as described above for the UK Biobank) was extracted directly from medical records for all cases. We searched the National Death Index for deaths among non-respondents to follow-up questionnaires, but the majority of deaths were reported by the postal service and next-of-kin. We have demonstrated in prior validation studies that these methods identify more than 98% of the deaths in the two cohorts (21).

Cholesterol and Triglyceride Assessment—Levels of TC, HDL-C, and TG were directly measured from participant blood samples at the Nutritional Biomarker Laboratory at the Harvard T.H. Chan School of Public Health, which participates in the CDC's Lipid Standardization Program for external validation. TC and TG were measured by enzymatic assay (Thermo Scientific, Waltham, Massachusetts, United States). HDL-C was determined by the same cholesterol reagent following precipitation of apoB-containing lipoproteins by dextran sulfate (MW ~50,000, VWR Cat# IC16011050) and magnesium chloride (Sigma Cat# M0250). Levels of LDL were calculated from these measurements using the Friedewald formula (22). CVs were computed for each assay and demonstrated acceptable accuracy (in HPFS, overall CV was 3.78% or TC, 7.4% for HDL-C, and 6.9% for TG; in NHS, 10.8% for TC, 6.4% for HDL-C, and 13.5% for TG).

Statistical Analyses—We used the quartile cutpoints in the UK Biobank to create four categories for each biomarker in the NHS and HPFS to improve comparability between the analyses in each cohort. The different distributions of the biomarkers in the UK Biobank and NHS/HPFS, coupled with the small sample size in the NHS/HPFS study, resulted in sparse data in the highest two quartiles for some lipids. Therefore, we combined quartiles three and four into one category in NHS/HPFS for each biomarker.

To examine the associations between lipid levels and glioma, we analyzed the case-control pairs in HPFS and NHS separately using conditional logistic regression, and then pooled their risk estimates using fixed effects models. In addition to the analyses being conditioned on the matching factors, we further adjusted for history of diabetes (yes vs. no), history of hypertension (yes vs. no), BMI (continuous), smoking status (never vs. past vs. current), and statin use (current use vs. no current use, only in HPFS). All covariates were selected from the most recent questionnaire prior to blood draw. Information on statin use was not collected in NHS prior to the blood collection in 1989 and was therefore not included in the NHS model. Tests of linear trend in glioma risk for higher levels of circulating lipids were assessed by assigning the median duration of the biomarker for each category, and treating those as a single continuous variable in the regression models.

We also analyzed NHS and HPFS separately to examine whether associations for each lipid measure differed between women (NHS) and men (HPFS). Although the cohorts differ in age at recruitment, with matching on age and multivariable adjustment, these results are comparable to the sex-stratified results of the UK Biobank. We tested whether the results differed by sex by computing a p-heterogeneity for each measure when pooling according to the fixed effect model.

All statistical analyses in the three cohorts were performed in SAS 9.4 (SAS Institute, Cary, NC) or R version 3.6.1, and all p-values were derived from two-sided tests.

Results

UK Biobank

During 2,358,964 person-years of follow up, 490 cases of glioma (188 women, 302 men) were identified in the UK Biobank. Compared to the full cohort, glioma cases were on

average older and more likely to be male and white (Table 1). Mean time from blood sample collection to glioma diagnosis was 3.8 years (IQR: 2.2 months to 9.0 years). Concentrations of TC, HDL-C, and LDL-C were slightly higher in women than in men, while TG concentrations were slightly higher in men than in women (Supplementary Table 1). There were no significant associations between circulating TC, HDL-C, LDL-C, or TG and glioma risk in age- and sex-adjusted or multivariable-adjusted models (Table 2). Compared to those in the lowest quartile, those in the highest quartile of TC (MV HR=1.20, 95%CI: 0.89-1.61, p-trend=0.24), HDL-C (MV HR=0.98, 95%CI: 0.71-1.36, p-trend=0.97), LDL-C (MV HR=1.14, 95%CI: 0.85-1.54, p-trend=0.35), and TG (MV HR=1.06, 95%CI: 0.80-1.41, p-trend=0.80) did not have significantly different risk of glioma. There was minimal evidence of confounding by the included covariates.

Results were similarly nonsignificant when stratified by sex (Supplementary Table 2). Results for GBM (n=342) and non-GBM cases (n=119) were also not statistically significant for any lipid measure (Supplementary Table 3), nor were the results when restricted to non-users of statins at baseline in an attempt to account for a possible effect of statin therapy (n=371, Supplementary Table 4).

After applying a four-year lag (50% of cases excluded), TC in the highest quartile was significantly associated with increased risk of glioma compared to the lowest quartile (MV HR=1.86, 95%CI 1.21-2.88, p-trend=0.005, Table 3). There was a trend toward higher glioma risk for those in the highest compared to lowest quartile of HDL-C (MV HR=1.49, 95%CI: 0.93-2.37, p-trend=0.09) and LDL-C (MV HR=1.33, 95%CI: 0.87-2.04, p-trend=0.10), but not for TG (MV HR=0.88, 95%CI: 0.60-1.31, p-trend=0.48). Upon stratification by sex, we observed significant associations between cholesterol and glioma risk in men only. Comparing the highest to the lowest quartile, TC (MV HR=2.26, 95%CI: 1.32-3.89, p-trend=0.002) and HDL-C (MV HR=2.34, 95%CI: 1.34-4.11, p-trend=0.006) were each associated with increased glioma risk among men. Higher LDL-C trended towards significantly higher risk of glioma (MV HR=1.53, 95%CI: 0.89-2.64 comparing highest to lowest quartile, p-trend=0.07). Among women, TC (MV HR=1.28, 95%CI: 0.61-2.68, p-trend=0.72), HDL-C (MV HR=0.87, 95%CI: 0.38-2.00, p-trend=0.53), and TG (MV HR=1.00, 95%CI: 0.52-1.91, p-trend=0.99) in the highest quartile were not significantly associated with glioma risk compared to the lowest quartile. In lagged models restricted to non-statin users at baseline (n=371), the results were not materially changed from the lagged analyses presented for the whole cohort (data not shown). In lagged models, results for TC, HDL-C, and LDL-C were each stronger for GBM than for non-GBM (Supplementary Table 5).

To follow up previous investigations into the association between statin use and glioma risk, we examined baseline current statin use as a main exposure in a separate analysis. No significant associations were observed between statin use and glioma risk overall (MV HR=1.04, 95%CI: 0.81-1.33 comparing current use to no current use), after applying a four year lag (MV HR=1.05, 95%CI: 0.73-1.50 comparing current use to no current use), stratified by sex, or for GBM and non-GBM separately (Supplementary Table 6).

NHS and HPFS

This study included 52 cases and 104 controls from NHS and 32 cases and 64 controls from HPFS (Table 1, Supplementary Table 1). The median time from blood sample collection to diagnosis was 9.3 years in NHS and 6.3 years in HPFS. The distribution of cholesterol and TG concentrations were lower on average than those found in UK Biobank.

No statistically significant associations were observed between each circulating lipid measure and glioma risk in combined analyses of the two studies. Only HDL-C showed a suggestive trend of reduced risk with increasing concentrations (MV OR=0.61, 95%CI: 0.23-1.63 comparing ≥54 to <45 mg/dL, p-trend=0.10, Table 2). No clear patterns were observed for TC, LDL-C, or TG, or for any of the measures when examined separately in women and men (Supplementary Table 2). When restricted to GBM cases (n=54), the risk of glioma was not significantly different for any of the lipids (for example, MV OR=0.72, 95%CI: 0.28-1.86 comparing TC ≥248 to <190 mg/dL, p-trend=0.48). Non-GBM cases were not analyzed separately due to the low number of cases (n=30). A four year lagged analysis in NHS/HPFS resulted in exclusion of 17 case/control sets (eight in NHS and nine in HPFS), and did not materially change the results (data not shown).

Discussion

In this study, we carried out several analyses in parallel, aimed at examining the association between prediagnostic lipids and glioma risk. These included a prospective cohort investigation in the UK Biobank and a matched, nested case-control analysis in the prospective NHS/HPFS. In both the UK Biobank and NHS/HPFS, no significant associations were observed for TC, HDL-C, LDL-C, or TG concentrations and glioma risk overall. Secondary analyses in the UK Biobank of non-users of statins at baseline and by glioma subtype did not materially change the results. However, in the UK Biobank, after implementation of a four year lag, higher levels of circulating cholesterol (specifically, TC and HDL-C and, to a lesser extent, LDL-C) were associated with a significantly higher risk of glioma, particularly among men and for GBM. These analyses were not conducted in NHS/HPFS due to limited sample size.

Our findings demonstrating a positive association of serum cholesterol with glioma after applying a four-year lag to limit the potential for reverse causation align with some (3–5) though not all (6–8) previous studies that have examined the association. In the 1980s and early 1990s, at least five studies were carried out attempting to identify an association between cholesterol levels and brain tumor risk. Three of these identified a positive association between higher total cholesterol levels and higher risk of brain tumors (3–5). In one of these studies, the association was limited to meningioma (4). A separate study that also included multiple brain tumor types (38% glioma) identified a similar positive association (5). In a later study that included a higher proportion of malignant brain tumors such as those studied in this report (61%), no association between total cholesterol and brain tumor risk was identified (7). Compared to the recent Mendelian randomization analysis by Saunders et al. that demonstrated no association between genetically-determined cholesterol and glioma risk, the present analysis, which used directly measured cholesterol

levels, demonstrated significant associations between TC and HDL-C and, to a lesser extent, LDL-C and glioma risk after applying a four-year lag (8, 23).

The current study differs from our prior report (2) that found an overall inverse association between self-reported hyperlipidemia and glioma risk in the NHS and HPFS that was confined to the first four years of follow up with no association apparent after a four year lag. By contrast, the present results from the UK Biobank based on serum levels showed a positive association between cholesterol and glioma risk only after a four year lag. Consistent with our earlier report, we found a non-significant inverse association for TC in the first four years of follow-up, though this was observed only in men (data not shown). Possible explanations for these different results across studies include the use of different definitions of hyperlipidemia (i.e., self-report of hyperlipidemia vs. measured cholesterol levels) or population differences between cohorts from the United States and the United Kingdom. On the other hand, the finding in our prior study of higher glioma risk with use of statins, which is a marker of high cholesterol, may be congruent with the current findings of elevated risk with increasing TC in the lagged analysis.

Although population-level studies remain mixed on the association between cholesterol and glioma risk, laboratory evidence has consistently demonstrated an important role for cholesterol in glioma metabolism (24, 25). A recent study by Villa et al. demonstrated, in vitro, that GBM is dependent on cholesterol for survival and is selectively vulnerable to treatment with liver X receptor (LXR) agonists in a cholesterol-dependent fashion (24). However, although the brain contains a large supply of the body's cholesterol stores, the majority of that cholesterol is synthesized in situ by astrocytes, making it unclear whether central nervous system malignancies are reliant on circulating levels of cholesterol for metabolism (26, 27). Because there have been few identified risk factors and no clinically meaningful circulating biomarkers for glioma risk, the exploration of cholesterol, a ubiquitous and inexpensive clinical biomarker, could prove meaningful for risk stratification. In addition, the in vitro evidence of a dependence for GBM on cholesterol could play a role in eventual therapeutics.

Strengths of our analysis include the multiple lines of evidence we have presented, as well as the large size of the UK Biobank, resulting in substantial numbers of glioma cases. The large number of participants with measured cholesterol levels is also a unique benefit of using UK Biobank data. Among participants in NHS and HPFS, the median time to diagnosis from blood sample collection was relatively long (median 7.2 years) and in all three cohorts, an appreciable number of glioma cases were diagnosed beyond an arbitrary four year window enabling performance of lagged analyses that limited protopathic bias in results. In addition, the study employed three separate cohort studies based in several different areas (the US, England, Wales and Scotland), enhancing generalizability of our findings. In NHS and HPFS, strengths include carefully confirmed cases by independent medical record review. In both cohorts, detailed questionnaires provided high-quality covariate data for multivariable adjustment.

Limitations of our study include the relatively limited power, especially for the NHS/HPFS and for subgroup analyses (e.g., when applying a 4-year lag, when restricting by tumor

subtype) in the UK Biobank, as well as the limited racial and ethnic diversity of the three cohorts, which all include mainly Caucasian participants. Analyses in the NHS/HPFS were especially limited by power, and null results in these analyses should therefore be interpreted with caution. Additionally, we were unable to assess whether changes in cholesterol over time were associated with glioma incidence as only a single cholesterol measurement was available for analysis. In NHS and HPFS, LDL was estimated using the Friedewald equation and, although relatively reliable, the Friedewald equation has been shown to be less accurate at high levels of TG and in patients who are non-fasting (28). Although TG levels were relatively low in the Harvard cohorts, 30% of samples were non-fasting, which may have affected the accuracy of calculated LDL values.

Some additional methodological challenges should be noted. In the UK Biobank, there were more cases among men than among women after applying a four-year lag. The opposite was true in the Harvard cohorts, where there were nearly twice as many participants from the female cohort, NHS, as there were from the male cohort, HPFS, suggesting a mismatch in statistical power for the gender-stratified analyses when comparing the two cohorts. Furthermore, the distribution of cholesterol levels differed between US and UK-based cohorts with, on average, higher cholesterol levels in the UK Biobank than in the Harvard cohorts. As a result of these differences, as well as the limited sample in the NHS/HPFS, combining the two highest quartiles of cholesterol levels was necessary in the Harvard cohorts.

Conclusion

In the UK Biobank, higher prediagnostic TC and HDL-C levels were associated with higher risk of glioma in four-year lagged analyses, but not in non-lagged analyses, in men only. These findings merit further investigation, given that there are few risk factors and no reliable biomarkers of risk identified for glioma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Characteristics of participants in the UK Biobank and Nurses' Health Study/Health Professionals Follow-Up Study.

	UK Biobank		NHS/HPFS	
Characteristic	**Full Cohort (n=405,263)**	**Glioma Cases (n=490)**	**Glioma Cases (n=84)**	**Controls (n=168)**
Age (years, median, IQR)	61 (56-65)	57 (49-62)	61 (53-65)	61 (53-65)
Male (n, %)	302 (61.6)	188117 (46.4)	32 (38.1)	64 (38.1)
Year of blood collection	2006-2010		NHS, 1989-90; HPFS, 1993-95	
Time from blood collection to glioma diagnosis (median, range)	3.8 (2.2-9.0)		7.2 (0.3-20.6)	
Body mass index (kg/m^2, median, IQR)	26.7 (24.5-29.8)	26.7 (24.1-29.9)	24.2 (21.9-27.2)	25.5 (22.7-28.3)
Race (n, %) *				
White	476 (97.1)	379,668 (93.7)	38 (45.2)	153 (91.1)
Non-white	8 (1.6)	24,162 (6.0)	2 (2.4)	0
Missing	6 (1.2)	1,433 (0.4)	44 (52.4)	15 (8.9)
Education (n, %) ^				
Secondary school	110 (22.4)	108,129 (26.7)	0	0
Vocational training	22 (4.5)	20,230 (5.0)	0	0
Some college	78 (15.9)	71,823 (17.7)	84 (100)	168 (100)
Completed college	164 (33.5)	132,741 (32.8)	0	0
None of the above	101 (20.6)	65,167 (16.1)	0	0
Missing	15 (3.1)	7,173 (1.8)	0	0
TC (mg/dL, median, IQR)	220.4 (190.6-249.4)	220.2 (190.0-248.1)	194.9 (169.9-217.2)	196.1 (173.8-220.2)
HDL-C (mg/dL, median, IQR)	54.9 (44.9-62.3)	54.1 (45.2-64.6)	48.5 (40.4-58.8)	50.9 (40.8-61.5)
LDL-C (mg/dL, median, IQR)	138.4 (114.5-160.1)	136.1 (114.1-159.1)	125.7 (98.0-142.0)	119.7 (96.9-143.1)
TG (mg/dL, median, IQR)	138.4 (97.3-198.0)	130.7 (91.9-189.6)	100.1 (68.4-149.2)	96.5 (69.6-139.7)
History of hypertension (n, %)				
Yes	151 (30.8)	105,647 (26.1)	22 (26.2)	35 (20.8)
No	336 (68.6)	298,812 (73.7)	62 (73.8)	133 (79.2)
Missing	3 (0.61)	804 (0.2)	0	0
History of diabetes (n, %)				

	UK Biobank		NHS/HPFS	
Characteristic	**Full Cohort (n=405,263)**	**Glioma Cases (n=490)**	**Glioma Cases (n=84)**	**Controls (n=168)**
Yes	28 (5.7)	20,578 (5.1)	2 (2.4)	6 (3.6)
No	460 (93.9)	383,693 (94.7)	82 (97.6)	162 (96.4)
Missing	2 (0.4)	992 (0.2)	0	0
Statin use (n, %)†				
Current statin use	101 (20.6)	59,707 (14.7)	3 (3.6)	4 (2.4)
No current statin use	389 (79.4)	345,171 (85.2)	29 (34.5)	60 (35.7)
Missing	0	385 (0.1)	52 (61.9)	104 (61.9)

Abbreviations: HDL-C: high-density lipoprotein cholesterol, HPFS: Health Professionals Follow-Up Study, IQR: interquartile range, LDL-C: low-density lipoprotein cholesterol, NHS: Nurses' Health Study, TC: total cholesterol, TG: triglycerides

*Race was not assessed in NHS until the 2004 questionnaire, and is presented here for all participants who survived to complete the 2004 questionnaire.

^Although not assessed explicitly in NHS and HPFS, all participants in the cohorts had at least some college education, and are indicated as such in the table.

†Variable was not assessed in the NHS.

Table 2.

Risk of glioma in the UK Biobank and Nurses' Health Study/Health Professionals Follow-Up Study by cholesterol concentrations, age- and sex-adjusted and multivariable adjusted.

			UK Biobank					NHS/HPFS[%]				
	Quartile	**Range (mg/dL)[*]**	**Cases[^]**	**HR[†]**	**95%CI**	**MV HR[‡]**	**95%CI**	**Cases**	**OR[**]**	**95%CI**	**MV OR[**,^^]**	**95%CI**
TC	Q1	<190	113	Ref.		Ref.		38	Ref.		Ref.	
	Q2	190-218	110	1.18	0.90-1.54	1.13	0.85-1.49	28	1.01	0.55-1.86	0.98	0.51-1.87
	Q3	218-248	119	1.26	0.97-1.64	1.21	0.90-1.62	18	0.77	0.38-1.56	0.74	0.34-1.62
	Q4	≥248	119	1.25	0.96-1.63	1.20	0.89-1.61					
	P-trend		461		0.09		0.24	84		0.56		0.54
HDL-C	Q1	<45	107	Ref.		Ref.		33	Ref.		Ref.	
	Q2	45-54	108	1.11	0.85-1.45	1.05	0.80-1.38	22	0.97	0.51-1.86	0.82	0.40-1.68
	Q3	54-65	109	1.20	0.91-1.58	1.13	0.85-1.50	29	0.76	0.35-1.64	0.61	0.23-1.63
	Q4	≥65	88	1.09	0.80-1.48	0.98	0.71-1.36					
	P-trend		412		0.54		0.97	84		0.41		0.10
LDL-C	Q1	<114	114	Ref.		Ref.		37	Ref.		Ref.	
	Q2	114-136	106	1.11	0.84-1.45	1.05	0.79-1.40	18	0.97	0.49-1.94	0.92	0.44-1.94
	Q3	136-159	120	1.19	0.92-1.54	1.13	0.85-1.52	29	0.95	0.51-1.77	0.83	0.41-1.66
	Q4	≥159	120	1.19	0.92-1.55	1.14	0.85-1.54					
	P-trend		460		0.16		0.35	84		0.89		0.62
TG	Q1	<92	96	Ref.		Ref.		40	Ref.		Ref.	
	Q2	92-131	123	1.08	0.83-1.42	1.07	0.82-1.41	17	0.88	0.44-1.78	0.84	0.38-1.85
	Q3	131-190	115	0.96	0.73-1.26	0.97	0.73-1.28	27	1.18	0.62-2.24	1.58	0.77-3.25
	Q4	≥190	127	1.03	0.79-1.35	1.06	0.80-1.41					
	P-trend		461		0.99		0.80	84		0.66		0.26

[*] Quartiles for each cholesterol measure were computed using the distribution of values among participants in the UK Biobank.

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

[†] Adjusted for age and sex (male vs. female)

‡Additionally adjusted for race (White vs. non-White), education (secondary school vs. vocational training vs. some college vs. completed college vs. none of the above), history of hypertension (yes vs. no), history of diabetes (yes vs. no), BMI (≤25 kg/m^2 vs. 25-30 kg/m^2 vs. ≥30 kg/m^2), smoking status (never vs. past vs. current), and statin use (current use vs. no current use).

**Matched on age, cohort, fasting status, month of sample collection, and racial and ethnic background.

^^Adjusted for history of hypertension (yes vs. no), history of diabetes (yes vs. no), BMI (continuous), smoking status (never vs. past vs. current), and statin use (current use vs. no current use).

%Computed from NHS and HPFS case-control study estimates using fixed effect meta-analysis.

Abbreviations: BMI: body mass index, HDL-C: high-density lipoprotein cholesterol, HPFS: Health Professionals Follow-Up Study, HR: hazard ratio, LDL-C: low-density lipoprotein cholesterol, MV: multivariable, NHS: Nurses' Health Study, OR: odds ratio, TC: total cholesterol, TG: triglycerides

Table 3.

Risk of glioma in the UK Biobank by baseline cholesterol concentrations with a four year lag period, stratified by sex.

			Total			Male			Female		
	Quartile	**Range (mg/dL)***	**Cases^**	**MV HR†**	**95%CI**	**Cases^**	**MV HR†**	**95%CI**	**Cases^**	**MV HR‡**	**95%CI**
TC	Q1	<190	49	Ref.		35	Ref.		14	Ref.	
	Q2	≥190-218	53	1.39	0.91-2.12	30	1.30	0.76-2.22	23	1.40	0.69-2.84
	Q3	≥218-248	56	1.49	0.96-2.31	35	1.76	1.02-3.04	21	1.02	0.48-2.17
	Q4	≥248	71	1.86	1.21-2.88	40	2.26	1.32-3.89	31	1.28	0.61-2.68
	P-trend		229		0.005	140		0.002	89		0.72
HDL-C	Q1	<45	45	Ref.		37	Ref.		8	Ref.	
	Q2	≥45-54	54	1.27	0.85-1.92	36	1.29	0.81-2.07	18	1.03	0.44-2.40
	Q3	≥54-65	56	1.46	0.96-2.21	26	1.30	0.77-2.20	30	1.26	0.57-2.81
	Q4	≥65	49	1.49	0.93-2.37	22	2.34	1.34-4.11	27	0.87	0.38-2.00
	P-trend		204		0.09	121		0.006	83		0.53
LDL-C	Q1	<114	56	Ref.		37	Ref.		19	Ref.	
	Q2	≥114-136	44	0.94	0.61-1.45	27	0.98	0.57-1.69	17	0.85	0.43-1.71
	Q3	≥136-159	62	1.23	0.81-1.87	36	1.39	0.81-2.38	26	0.99	0.50-1.95
	Q4	≥159	66	1.33	0.87-2.04	39	1.53	0.89-2.64	27	1.01	0.51-2.01
	P-trend		228		0.10	139		0.07	89		0.82
TG	Q1	<92	53	Ref.		30	Ref.		23	Ref.	
	Q2	≥92-131	66	0.98	0.67-1.42	38	1.03	0.63-1.68	28	0.91	0.50-1.63
	Q3	≥131-190	48	0.69	0.46-1.04	29	0.64	0.48-1.08	19	0.75	0.40-1.42
	Q4	≥190	62	0.88	0.60-1.31	43	0.82	0.50-1.34	19	1.00	0.52-1.91
	P-trend		229		0.48	140		0.33	89		0.99

*Quartiles for each cholesterol measure were computed using the distribution of values among participants in the UK Biobank.

^Cases may not sum to total due to missing cholesterol values.

†Adjusted for age, sex (male vs. female), race (White vs. non-White), education (secondary school vs. vocational training vs. some college vs. completed college vs. none of the above), history of hypertension (yes vs. no), history of diabetes (yes vs. no), BMI (≤25 kg/m^2 vs. 25-30 kg/m^2 vs. ≥30 kg/m^2), smoking status (never vs. past vs. current), and statin use (current use vs. no current use).

[‡]Adjusted for age, sex (male vs. female), race (White vs. non-White), education (secondary school vs. vocational training vs. some college vs. completed college vs. none of the above), history of hypertension (yes vs. no), history of diabetes (yes vs. no), BMI (≤25 kg/m^2 vs. 25-30 kg/m^2 vs. ≥30 kg/m^2), and smoking status (never vs. past vs. current).

Abbreviations: BMI: body mass index, CI: confidence interval, HDL-C: high-density lipoprotein cholesterol, HR: hazard ratio, LDL-C: low-density lipoprotein cholesterol, MV: multivariable, TC: total cholesterol, TG: triglycerides