



Adiposity at different periods of life and risk of adult glioma in a cohort of postmenopausal women

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ABSTRACT

Background: Little is known about risk factors for adult glioma. Adiposity has received some attention as a possible risk factor.

Methods: We examined the association of body mass index (BMI), waist circumference (WC) and waist-to-hip ratio (WHR), measured at enrollment, as well as self-reported weight earlier in life, with risk of glioma in a large cohort of postmenopausal women. Over 18 years of follow-up, 217 glioma cases were ascertained, including 164 glioblastomas. Cox proportional hazards models were used to estimate hazard ratios and 95% confidence intervals.

Results: There was a modest, non-significant trend toward increasing risk of glioma and glioblastoma with increasing measured BMI and WHR. No trend was seen for WC. Self-reported BMI earlier in life showed no association with risk.

Conclusions: Our weak findings regarding the association of adiposity measures with risk of glioma are in agreement the results of several large cohort studies. In view of the available evidence, adiposity is unlikely to represent an important risk factor for glioma.

1. Introduction

Gliomas are the most common primary intracranial cancer and the most fatal type of brain tumor [1]. Little is known about risk factors for gliomas [2]. Established risk factors include several rare, inherited genetic syndromes and exposure to ionizing radiation [2]; however, these account for only a small proportion of gliomas.

Adiposity has received attention as a possible risk factor for glioma [3–10]. Such an association might be mediated by circulating insulin levels, since hyperinsulinemia is common among obese and sedentary individuals, and insulin has pro-mitotic properties [4,5]. Insulin crosses the blood-brain barrier, and insulin's actions within the CNS are mediated by two canonical pathways involved in carcinogenesis [11]. However, most studies have found little evidence of an association with adiposity. Of two meta-analyses of the association of adult body mass index (BMI) and glioma, one found no association in men or women [9], whereas the other reported a significant association in women but not in men [8]. Two other studies [4,5] showed positive associations of BMI at age 18 and 21, respectively, with glioma risk, raising the possibility of an etiologic role of obesity earlier in life.

We examined the association of BMI, waist circumference (WC), and waist-to-hip ratio (WHR) measured at enrollment with risk of glioma in

a large cohort of postmenopausal women. Additionally, we assessed the association of BMI at age 18, 35, and 50 with risk of glioma in a subset of the study population.

2. Methods

The Women's Health Initiative is a large, multicenter study designed to advance understanding of the determinants of major chronic diseases in postmenopausal women. It is composed of a clinical trial component (CT, $n = 68,132$) and an observational study component (OS, $n = 93,676$) [12]. Women between the ages of 50 and 79 and representing the major racial/ethnic groups were recruited from the general population at 40 clinical centers throughout the US between 1993 and 1998.

At study entry, self-administered questionnaires were used to collect information on demographics, medical, reproductive, and family history, and lifestyle factors, including smoking history, alcohol consumption, diet, and recreational physical activity. All participants had their weight and height measured by trained staff at baseline. Weight was measured to the nearest 0.1 kg, and height to the nearest 0.1 cm. Body mass index was computed as weight in kilograms divided by the square of height in meters. Waist circumference and waist-to-hip ratio

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Table 1
Association of baseline anthropometric measures with risk of glioma and glioblastoma in the Women's Health Initiative (n = 161,119^a).

BMI (kg/m ²) ^b	Glioma (n cases = 217)				Glioblastoma (n cases = 164)			
	N cases	N non-cases	HR ^d	95% CI	N cases	N non-cases	HR ^d	95% CI
18.5– < 25.0	70	54,827	1.00	Ref.	53	54,827	1.00	Ref.
25.0– < 30.0	74	55,571	1.06	0.76–1.47	54	55,571	1.04	0.71–1.53
30.0– < 35.0	43	29,684	1.21	0.81–1.79	33	29,684	1.25	0.79–1.97
≥ 35.0	25	18,582	1.30	0.81–2.08	20	18,582	1.46	0.86–2.50
Missing	5	106			4	106		
<i>P for linear trend</i>			0.32				0.18	
Waist circumference (cm)								
< 76.0	50	40,525	1.00	Ref.	33	40,525	1.00	Ref.
76.0– < 84.5	60	40,226	1.18	0.80–1.73	48	40,226	1.44	0.92–2.25
84.5– < 95.0	57	39,395	1.24	0.84–1.83	42	39,395	1.38	0.86–2.20
≥ 95.0	50	40,756	1.11	0.74–1.68	41	40,756	1.41	0.87–2.29
<i>P for linear trend</i>			0.66				0.25	
WHR ^c								
< 0.76	47	39,855	1.00	Ref.	33	39,855	1.00	Ref.
0.76– < 0.80	59	39,846	1.22	0.83–1.80	44	39,846	1.28	0.81–2.01
0.80– < 0.86	53	40,044	1.22	0.82–1.81	41	40,044	1.30	0.82–2.06
≥ 0.86	56	39,725	1.34	0.90–2.00	44	39,725	1.45	0.92–2.30
Missing	2	694			2	694		
<i>P for linear trend</i>			0.17				0.09	

Abbreviations: HR—hazard ratio; 95% CI—95% confidence interval; BMI—body mass index; WHR—waist-to-hip ratio.

^a Women with anthropometric measurements.

^b 2,132 women with BMI < 18.5 or BMI missing.

^c 740 women missing WHR measurement.

^d Adjusted for age, smoking status, alcohol intake, physical activity, hormone therapy, years of education, ethnicity, and treatment status.

were also measured. Questions about physical activity at baseline referred to a woman's usual pattern of activity, including walking and recreational physical activity. A variable "current total leisure-time physical activity" (MET-hours/week) was computed by multiplying the number of hours per week of leisure-time physical activity by the metabolic equivalent (MET) value of the activity and summing over all types of activities [13].

BMI, which reflects overall adiposity, was categorized according to the WHO classification: 18.5– < 25.0 kg/m² – normal weight, 25.0– < 30.0 kg/m² – overweight, and ≥ 30.0 kg/m² – obese. Waist circumference (WC), a measure of central adiposity, and waist-to-hip ratio (WHR), a measure of the ratio of central to lower extremity adiposity, were categorized into quartiles based on the distribution among non-cases. Information on weight at earlier ages was available only for participants in the Observational Study (n = 92,557) and was used to compute BMI at ages 18, 35, and 50. For this analysis, owing to the reduced sample size, we created tertiles based on the distribution in non-cases.

Clinical outcomes (including new cancer diagnoses) were updated semiannually in the CT and annually in the OS using in-person, mailed, or telephone questionnaires. Self-reports of malignancy, including gliomas, were verified by central review of medical records and pathology reports by trained physician adjudicators [14]. Among 161,119 WHI participants with anthropometric measurements, 217 cases of glioma were ascertained over a median of 17.8 years of follow-up. Of these, 164 had glioblastoma. Other gliomas included: mixed glioma, ependymoma NOS, well-differentiated low-grade astrocytoma, anaplastic astrocytoma, and oligodendroglioma.

2.1. Statistical analysis

Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CI) for the association of anthropometric factors with risk of glioma and glioblastoma, using days to event as the timescale. Participants who had not developed glioma by the end of follow-up, who had died, or who withdrew from the study before the end of follow-up were censored. Cases contributed person-

time to the study from their date of enrollment until the date of diagnosis, and non-cases (participants who were censored) contributed person-time from their date of enrollment until the end of follow-up, date of death, or date of withdrawal from the study, whichever came first. Hazard ratios were computed by quartile of measured anthropometric variables and by tertiles of self-reported body weight at earlier ages. Covariates were selected for inclusion in the final model if their inclusion changed the parameter estimate by > 10%. Pack-years of smoking and use of hormone therapy did not improve the model and were excluded. The final model included age (continuous), smoking status (never, former, current), alcohol intake (servings/week – continuous), physical activity (metabolic equivalent tasks [MET]-hrs/wk continuous), years of education (less than high school, high school graduate/some college, college graduate, post-college), ethnicity (white, black, other), and allocation in the clinical trial arms or observational study. A test for linear trend over quantiles of anthropometric variables was performed by assigning the median value to each category and modeling this variable as a continuous variable. In order to account for women with a prevalent cancer at the time of enrollment, we carried out a sensitivity analysis in which we excluded women who reported a history of cancer at entry into the study. We tested the proportional hazards assumption using PROC LIFETEST (SAS Institute). The formal test for non-proportional hazards was not significant and the log-log survival plots did not indicate any marked deviation from normality. All analyses were performed in SAS 9.4 (SAS Institute, Cary, NC). All P-values are 2-sided.

3. Results

Glioma cases did not differ from non-glioma cases in terms of mean age, smoking status, mean pack-years of smoking, alcohol intake, hormone therapy, or physical activity. The proportion of whites was higher among cases than among non-cases (93.5 vs. 82.7 percent, p = 0.0002).

In multivariable-adjusted analyses, HRs for glioma and, particularly glioblastoma were somewhat elevated for the highest quartiles of the anthropometric measures of interest (Table 1). There was a suggestion of a non-significant trend, particularly for the association of BMI with

Table 2Association of self-reported weight at different ages with risk of glioma in the Observational Study component of the Women's Health Initiative (n = 91,150^a).

	Glioma (n cases = 115)				Glioblastoma (n cases = 86)			
			HR ^b	95% CI			HR ^b	95% CI
BMI (kg/m ²) at age 18								
< 19.4	31	30,465	1.00	Ref.	25	30,465	1.00	Ref.
19.4–21.3	45	30,822	1.28	0.81–2.03	33	30,822	1.11	0.71–1.72
≥ 21.3	39	29,731	1.28	0.80–2.04	28	29,731	1.01	0.63–1.61
<i>P for linear trend</i>			0.33				0.97	
BMI (kg/m ²) at age 35								
< 20.8	37	30,352	1.00	Ref.	28	30,352	1.00	Ref.
20.8– < 22.9	43	30,122	1.14	0.73–1.77	31	30,122	1.11	0.71–1.72
≥ 22.9	35	30,472	1.04	0.65–1.66	27	30,472	1.01	0.63–1.61
<i>P for linear trend</i>			0.92				0.99	
BMI (kg/m ²) at age 50								
< 22.1	39	30,254	1.00	Ref.	30	30,254	1.00	Ref.
22.1– < 25.1	47	30,328	1.21	0.79–1.86	35	30,328	1.17	0.72–1.92
≥ 25.1	28	30,454	0.84	0.51–1.39	21	30,454	0.87	0.49–1.56
<i>P for linear trend</i>			0.46				0.60	

Abbreviations: HR – hazard ratio; 95% CI – 95% confidence interval; BMI – body mass index.

^a Women with self-reported weight earlier in life.^b Adjusted for age, smoking status, alcohol intake, physical activity, years of education, and ethnicity.

glioblastoma and for WHR with glioma and glioblastoma. WC showed no association with glioma, and HRs for glioblastoma were similar for quartiles 2 to 4, showing no trend. None of the point estimates was statistically significant, and none of the linear trends over quartiles was significant. Associations with self-reported body weight at earlier points in life (ages 18, 35, and 50), available on a subset of the population (WHI observational study), showed no suggestion of an increasing trend with either glioma or glioblastoma (Table 2). When measured BMI, WC, and WHR were reanalyzed in this subgroup, no suggestive associations or trends were seen for glioma or glioblastoma.

In the sensitivity analysis excluding women with prevalent cancer, the associations with measured BMI, WC, and WHR with glioma and glioblastoma were either unchanged or slightly attenuated (data not shown). In particular, the monotonic trend for WHR with glioblastoma was weakened (HR for 2nd to 4th quartiles: 1.32, 95% CI 0.82–2.14, 1.27, 95% CI 0.77–2.07, 1.35, 95% CI 0.82–2.23, respectively; *p* for linear trend 0.30).

4. Discussion

In this large prospective study of postmenopausal women, there was a suggestion of a modest and non-significant positive association of measured BMI and WHR, but not WC, with risk of glioma and glioblastoma. Self-reported BMI earlier in life showed no association with risk of adult glioma or glioblastoma.

Previous studies have found little evidence of an association of adiposity with glioma. A meta-analysis [9] of 5 studies (4 cohort, 1 case-control) with a total of 2,725 cases of glioma, showed that BMI was not associated with glioma: the summary relative risk (RR) for overweight vs. normal weight was 1.06 (95% CI 0.94–1.20) and RR for obesity was 1.11 (95% CI 0.98–1.27). The second meta-analysis [8], which included only 3 studies (2 cohort and 1 case-control) with 2,418 cases of glioma, reported a positive summary association of BMI in females (odds ratio/relative risk 1.17, 95% CI 1.03–1.32), but not in males. However, this result appears to stem from two errors, which appear in Fig. 5 of the publication [8]. First, the meta-analysis included results for “BMI at age 21,” rather than “BMI in recent past” from the Little et al. study [5]. BMI at age 21 showed a borderline significant positive association, whereas BMI in recent past showed no association (see Table 2, p. 1029 [5]). It is BMI in midlife that is the focus of the meta-analyses. Second, the authors included data from an analysis of the Nurses' Health Study I by Holick et al. [15]. However, this paper

presented data on intake of fruits, vegetables, and carotenoids, but not on BMI, in relation to glioma risk. (GCK contacted both the first and second authors on the paper, and they both confirmed that their data on BMI and glioma risk were not published). Therefore, the source of the data for the two entries from the Holick et al. study (“Holick – NHS I, females, 2007, 25.0–29.9” and “Holick – NHS I, females, 2007, ≥ 30.0”) is unclear.

Since publication of the meta-analyses, results from a large Norwegian cohort study [10] with 4,382 cases of glioma showed no association of overweight or obesity with glioblastoma or any other glioma subgroup; however, information on socioeconomic status and other covariates was not available in this study.

Fewer studies have examined BMI in adolescence in relation to risk of adult glioma [4,5]. The large relative risk for obesity relative to normal BMI reported by Moore et al. [4] was based on 11 glioma cases, and there was no suggestion of an elevated risk in the overweight category. In the case-control study by Little et al. [5], none of the odds ratios for the 25–29.9 or ≥ 30 kg/m² categories was statistically significant in males or females, although the trend per unit increase in BMI was statistically significant in females but not in males.

In the present study, there was a suggestion of increased risk, particularly for glioblastoma in association with BMI and WHR, although the associations were not statistically significant due to small numbers. There was no evidence of an increasing trend for the association of WC with glioma or glioblastoma, in spite of the fact that measured WC is a reliable indicator of central adiposity [16]. When we used self-reported body weight at earlier time points, available on roughly half the study population, there were no clear trends with glioma or glioblastoma. This was also true when associations of measured BMI, WC, and WHR were examined in this subgroup. However, women in the observational study tended to have lower BMI compared to women in the clinical trials, and this could have obscured a positive association.

It should also be mentioned that gliomas are a heterogeneous group of tumors of different histopathologic types and different grades (1). Our results are driven by the results for glioblastoma, the largest single subgroup. However, the numbers of other types of glioma (diffuse astrocytomas, anaplastic astrocytomas, pilocytic astrocytomas, and oligodendrogliomas), were too small to analyze separately.

Strengths of the present study include the prospective nature of the study, central adjudication of all malignancies, standardized measurement of anthropometric factors at enrollment, and the availability of self-reported weight at earlier periods of life. Limitations include the

relatively small number of cases and the fact that, due to restriction of the study to postmenopausal women, glioma cases occurring in women below age 50 were not captured.

In conclusion, we found a suggestion of a modest positive association of measured BMI and WHR, but not WC, with risk of glioma and glioblastoma. Self-reported BMI earlier in life showed no association with increased risk. Based on available evidence, it is unlikely that adiposity represents an important risk factor for glioma.

Author's contributions

Conceived the study: Geoffrey Kabat, Thomas Rohan.

Designed the study: Geoffrey Kabat, Thomas Rohan.

Acquired the data: Geoffrey Kabat.

Analyzed the data: Geoffrey Kabat.

Wrote the first draft of the manuscript: Geoffrey Kabat.

Commented on and contributed additional ideas: Thomas Rohan.

Approved the final manuscript and conclusions: Geoffrey Kabat, Thomas Rohan.

Declaration of conflicting interests/disclosure

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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