Height, Body Mass Index, and Physical Activity in Relation to Glioma Risk

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Abstract

Whether energy balance during early life and/or adulthood is related to glioma risk is unknown. We therefore investigated height, body mass index (BMI), and physical activity in relation to glioma risk in the prospective NIH-AARP Diet and Health Study. Participants completed a baseline questionnaire (sent in 1995-1996) inquiring about height, weight, and potential confounders. A second questionnaire (sent in 1996) inquired about physical activity during ages 15 to 18, 19 to 29, and 35 to 39 years and the past 10 years and body weight at ages 18, 35, and 50 years. During follow-up from 1995/1996 to 2003, we documented 480 cases of glioma among 499,437 respondents to the baseline questionnaire and 257 cases among 305,681 respondents to the second questionnaire. Glioma risk among tall persons (≥1.90 m) was twice that of short persons [<1.60 m; multivariate relative risk (RR), 2.12; 95% confidence interval (95% CI), 1.18-3.81; P_{trend} = 0.006]. Risk among participants who were obese (BMI 30.0-34.9 kg/m^2) at age 18 years was nearly four times that of persons of normal weight (BMI 18.5-24.9 kg/m^2) at age 18 years (RR, 3.74; 95% CI, 2.03-6.90; P_{trend} = 0.003); 11 cases were obese at age 18 years. Risk among participants who were active during ages 15 to 18 years was 36% lower than that of persons who were inactive during ages 15 to 18 years (RR, 0.64; 95% CI, 0.44-0.93; P_{trend} = 0.02). BMI and physical activity after age 18 years were unrelated to glioma risk. Adult height, BMI during adolescence, and physical activity during adolescence were each associated with glioma risk, supporting a role for early-life energy balance in glioma carcinogenesis. [Cancer Res 2009;69(21):8349–55]

Introduction

Cancers of the brain and central nervous system result in an estimated 142,000 deaths per year worldwide (1) and 13,000 deaths per year in the United States (2). Gliomas, which include some of the most lethal types of cancer, account for >80% of brain and central nervous system cancers (3). The etiology of glioma among adults is poorly understood. Established risk factors for glioma include older age, male gender, Caucasian race/ethnicity, and rare genetic syndromes (4). The only known modifiable risk factor is high level of ionizing radiation, which accounts for only a small proportion of glioma cases (4).

Recently, tallness was identified as a possible risk factor for adult-onset glioma in the Million Women Study, with each 10 cm increase in height conferring an ∼20% increase in glioma risk (5). Potentially underlying this association may be that height is a marker for caloric intake relative to energy expenditure, that is, energy balance (6), during childhood. Although height is partly determined by genetic inheritance (7), natural history studies show that short stature can result from low caloric intake relative to caloric expenditure during growth. Such caloric deprivation explains why, for example, North Korean children are 8 cm shorter than their genetically similar but better nourished counterparts in South Korea (8).

Body mass index (BMI) and physical activity are also related to energy balance. Previous studies found no compelling evidence of an association between BMI or physical activity during adulthood and glioma risk (reviewed in ref. 5). However, to our knowledge, no study has examined BMI or physical activity during early life, which may be of greater etiologic relevance. We therefore investigated height, BMI during both adolescence and adulthood, and physical activity during adolescence and adulthood in relation to glioma risk in a cohort of ∼500,000 men and women.

Materials and Methods

The NIH-AARP Diet and Health Study was initiated in 1995 to 1996 when a baseline questionnaire inquiring about usual dietary intake, physical activity, and other health-related behaviors was sent to 3.5 million AARP members ages 50 to 71 years and residing in one of six states (California, Florida, Pennsylvania, New Jersey, North Carolina, and Louisiana) or two metropolitan areas (Atlanta, Georgia and Detroit, Michigan; ref. 9). A total of 566,402 AARP members completed the questionnaire satisfactorily. In late 1996, 334,908 participants responded to a second questionnaire that was mailed to those still living in a study area and having no prevalent cancer of the colon, breast, or prostate.

Of the 566,402 baseline questionnaire respondents, we excluded participants whose questionnaires were completed by proxy respondents (n = 15,760) or who had a previous diagnosis of cancer (n = 51,205). After exclusions, the analytic cohort consisted of 499,437 participants, including 305,681 persons who completed the second questionnaire. The NIH-AARP Diet and Health Study was approved by the Special Studies Institutional Review Board of the National Cancer Institute. All participants provided written informed consent.

Ascertainment and classification of brain cancer cases. Incident, first primary brain cancer cases (*International Classification of Diseases 10th Edition* codes C710-C719) were identified through December 31, 2003 by linking the cohort with eight state cancer registries serving our cohort and three additional states (Arizona, Nevada, and Texas). In a previous validation study, the sensitivity and specificity of cancer identification were estimated to be ∼90% and 99.5%, respectively (10). We defined gliomas as malignant brain neoplasms with a microscopically confirmed *International Classification of Diseases for Oncology,*

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doi:10.1158/0008-5472.CAN-09-1669

Table 1. Baseline characteristics according to adult height, BMI at age 18 years, and physical activity level at age 18 years

Characteristic	Adult height (m)			BMI at age 18 y (kg/m²)			Physical activity at age 18 y (MET-h/wk)	
	<1.60-1.69	1.70-1.74	≥1.75	<25.0	25.0-29.9	≥30.0	≤41.5	≥41.6
Participants (*n*)	188,860	81,585	223,450	240,320	25,597	4,478	147,079	143,484
Mean age (y)	62.1	62.1	61.9	62.3	61.5	60.9	62.8	62.9
Men (%)	14.0	66.5	95.7	58.5	76.7	60.9	56.8	60.3
Caucasian (%)	89.2	91.9	95.2	94.1	94.8	93.4	93.5	94.0
College education (%)	30.2	39.9	47.2	43.0	45.7	39.2	41.4	41.3
Married (%)	50.3	71.2	84.0	69.0	75.2	64.1	67.9	69.5
Mean adult height (m)	1.62	1.72	1.81	1.72	1.75	1.72	1.72	1.73
Mean baseline BMI (kg/m²)	27.1	27.0	27.2	26.6	30.3	32.9	26.8	27.1
Mean physical activity during past 10 years* (MET-h/wk)	34.8	33.4	33.0	34.0	32.2	29.4	28.5	39.0

NOTE: All values (except age) were directly standardized to the age distribution of the cohort.
*Data available only for those participants who completed the second questionnaire.

Third Edition histology codes between 9380 and 9480. We also examined an alternative definition using *International Classification of Diseases for Oncology, Third Edition* codes 9380 to 9460, but the number of cases was the same; therefore, results were identical. Because of potential etiologic heterogeneity, we conducted analyses specific to glioblastoma (codes 9440-9442), the most common and aggressive glioma subtype. However, findings for glioblastoma differed little from those of glioma; thus, we present these results only in brief. We determined vital status of study members by linking participant data to the U.S. Social Security Administration's Death Master file.

Assessment of height, body weight, and physical activity. At baseline, participants were asked to report their current height and body weight, which were used to calculate BMI at baseline. We grouped subjects according to five BMI (kg/m²) categories: <18.5 (underweight), 18.5 to 24.9 (normal weight), 25.0 to 29.9 (overweight), 30.0 to 34.9 (obese class I), and ≥35.0 (obese classes II and III; ref. 11). On the second questionnaire, participants reported their body weight at ages 18, 35, and 50 years and height at age 18 years. We calculated BMI at age 18 years using height at age 18 years and BMI at ages 35 and 50 years using current height reported from the baseline questionnaire. Participants also reported the amount of time spent in physical activities of a moderate/vigorous intensity (e.g., biking, fast walking, aerobics, and jogging/running) and light intensity (e.g., light housework, slow walking, and light gardening) at ages 15 to 18, 19 to 29, and 35 to 39 years and during the past 10 years. Participants selected their level of activity from six response options: never, rarely, weekly but <1 h/wk, 1 to 3 h/wk, 4 to 7 h/wk, and >7 h/wk. We calculated an index of physical activity at each age using the formula: hours of light physical activity * 3 metabolic equivalents (MET) + hours of moderate/vigorous activity * 5 METs. Our physical activity categories are based on approximate quintiles of physical activity across age groups of this MET-h/wk index (≤11.5, 11.6-29.0, 29.1-41.5, 41.6-51.5, and ≥51.6).

Statistical analysis. Participants were followed from the date of return of the baseline questionnaire until diagnosis of first cancer, death, move out of the cancer registry ascertainment areas, or date of last follow-up on December 31, 2003. For the BMI and physical activity analyses, which used data from the second questionnaire, participants were followed from the date that the second questionnaire was returned. Relative risks (RR) and 95% confidence intervals (95% CI) were estimated using Cox models

Table 2. Correlations between measures of height, BMI, and physical activity at specific ages

	Adult height	Height age 18 y	BMI age 18 y	BMI age 35 y	BMI age 50 y	BMI baseline age	Physical activity ages 15-18 y	Physical activity ages 19-29 y	Physical activity ages 35-39 y	Physical activity last 10 y
Adult height	1.00	0.93	0.06	0.11	0.04	−0.02	0.09	−0.03	−0.10	−0.04
Height at age 18 y		1.00	0.04	0.17	0.08	0.02	0.09	−0.03	−0.09	−0.04
BMI age 18 y			1.00	0.62	0.46	0.36	0.01	−0.02	−0.04	−0.03
BMI age 35 y				1.00	0.75	0.60	0.03	−0.03	−0.08	−0.08
BMI age 50 y					1.00	0.82	0.04	−0.01	−0.08	−0.16
BMI at baseline age						1.00	0.04	0.02	−0.05	−0.18
Physical activity ages 15-18 y							1.00	0.72	0.52	0.30
Physical activity ages 19-29 y								1.00	0.79	0.45
Physical activity ages 35-39 y									1.00	0.63
Physical activity last 10 y										1.00

with person-time as the underlying time metric. Tests of the proportional hazards assumption did not reveal departures from proportionality.

All multivariate models were adjusted for age at baseline, age-squared, gender, race/ethnicity (White, Black, other), highest attained level of education (did not complete high school, completed high school, some college, completed college), and marital status (married, divorced, separated, widowed, unmarried). Covariates were selected if previous brain cancer studies had indicated an association. We also examined smoking and alcohol intake, but these covariates had little effect on estimated associations and were not retained in the models. For covariates with incomplete data, we modeled nonresponse using indicator variables. Tests of linear trend were done by modeling the median value of each exposure category as a single continuous variable, with statistical significance evaluated by the Wald test. All P values are based on two-sided tests. Statistical analyses were done using SAS release 9.1.3 (SAS Institute).

Results

During up to 8.2 years of follow-up, we ascertained up to 480 cases of glioma, with 341 cases among men and 139 cases among women. Among 270,395 respondents to the second questionnaire with complete information on BMI at ages 18, 35, and 50 years and at the baseline age, we identified 236 cases of glioma. Among 290,563 respondents with complete information on physical activity at ages 15 to 18, 19 to 29, and 35 to 39 years and during the past 10 years, we identified 257 cases of glioma.

Baseline characteristics of our cohort according to adult height (the reported height at the time that the questionnaire was completed), BMI at age 18 years, and physical activity at age 18 years are described in Table 1. Taller persons were more likely to be men, to be Caucasian, to have a college education, and to be married. Participants who were obese (BMI ≥30.0 kg/m^2) at age 18 years were more likely to have a high baseline BMI and less likely to be married, to have a college education, and to be physically active during the past 10 years. Participants who were physically active at age 18 years were more likely to be physically active during the past 10 years.

Table 2 indicates the pairwise correlations between height, BMI, and physical activity. Adult height was strongly correlated with height at age 18 years (r = 0.93; participants' adult height was a mean of 0.1 cm greater than at age 18 years) but was not meaningfully associated with BMI or physical activity regardless of age. BMI values across the lifespan were intercorrelated, with strong correlations between adjacent age periods (r = 0.62-0.82) and moderate correlations between nonadjacent age periods (r = 0.36-0.60). Physical activity levels across the lifespan were also highly intercorrelated, with strong correlations between adjacent age periods (r = 0.63-0.79) and moderate correlations between nonadjacent age periods (r = 0.30-0.52). BMI at age 50 years and baseline BMI each had a modest inverse correlation with physical activity during the past 10 years (r = -0.16 and -0.18, respectively).

Taller participants were at greater risk for glioma (Table 3) and glioblastoma than shorter participants. In multivariate models, glioma and glioblastoma risk among participants with an adult height of ≥1.90 m was more than twice that of participants with an adult height of <1.60 m (glioma: RR, 2.12; 95% CI, 1.18-3.81; P_{trend} = 0.006; glioblastoma: RR, 2.12; 95% CI, 1.07-4.18; P_{trend} = 0.01). In analyses stratified by gender, statistically significant trends remained evident for both men (P_{trend} = 0.03) and women

Table 3. RR (95% CI) of glioma in relation to adult height (the reported height at the time that the questionnaire was completed)

Group	Adult height category (m)								P_{trend}
	<1.60	1.60-1.64	1.65-1.69	1.70-1.74	1.75-1.79	1.80-1.84	1.85-1.89	≥1.90	
All men and women									
No. cases	36	37	57	83	101	89	49	28	
Age- and sex-adjusted RR (95% CI)	1.00 (reference)	0.88 (0.56-1.39)	1.08 (0.70-1.65)	1.32 (0.84-2.05)	1.35 (0.85-2.16)	1.38 (0.85-2.23)	1.67 (0.99-2.81)	2.21 (1.25-3.92)	0.002
Multivariate RR* (95% CI)	1.00 (reference)	0.88 (0.56-1.39)	1.08 (0.70-1.66)	1.31 (0.84-2.05)	1.32 (0.82-2.13)	1.34 (0.82-2.18)	1.62 (0.95-2.75)	2.12 (1.18-3.81)	0.006
Men									
No. cases		26		57	94	87	49	28	
Age-adjusted RR (95% CI)		1.00 (reference)		1.08 (0.68-1.71)	1.16 (0.75-1.78)	1.17 (0.75-1.81)	1.44 (0.89-2.32)	1.95 (1.15-3.34)	0.01
Multivariate RR (95% CI)		1.00 (reference)		1.04 (0.65-1.66)	1.10 (0.71-1.71)	1.11 (0.71-1.73)	1.36 (0.84-2.21)	1.76 (1.02-3.06)	0.03
Women									
No. cases	33	35	36	26		9			
Age-adjusted RR (95% CI)	1.00 (reference)	0.97 (0.60-1.56)	1.08 (0.67-1.73)	1.55 (0.93-2.60)		1.53 (0.73-3.20)			0.06
Multivariate RR (95% CI)	1.00 (reference)	0.98 (0.61-1.58)	1.10 (0.68-1.77)	1.61 (0.96-2.71)		1.65 (0.78-3.48)			0.04

*Multivariate models are adjusted for age at baseline, age-squared, gender, race (White, Black, other), highest level of education (did not complete high school, completed high school, some college, completed college), marital status (married, divorced, separated, widowed, unmarried), and baseline BMI (<18.5, 18.5-24.9, 25.0-29.9, 30.0-34.9, ≥35.0 kg/m^2).

(P_{trend} = 0.04). In models of adult height as a continuous variable, each 10 cm increase in height was associated with an 18% increase in glioma risk (RR, 1.18; 95% CI, 1.02-1.36) among men and a 30% increase (RR, 1.30; 95% CI, 1.02-1.67) among women. Among participants with complete information on both adult height and height during late adolescence (age 18 years), each measure of height was similarly associated with glioma risk.

Persons who were obese at age 18 years had a substantially elevated glioma risk (Table 4; RR, 3.74; 95% CI, 2.03-6.90; P_{trend} = 0.003) and glioblastoma risk (RR, 3.53; 95% CI, 1.72-7.24; P_{trend} = 0.006) compared with persons of normal weight at age 18 years. Participants with a BMI ≥35 kg/m^2 at age 35 years were also at increased risk for glioma (RR, 4.05; 95% CI, 1.97-8.32; P_{trend} = 0.01) relative to participants of normal weight at this age. BMI at age 50 years and baseline BMI were not associated with either glioma or glioblastoma risk. We found no link between weight gain between ages 18 and 50 years and glioma risk. Participants with ≥20 kg weight gain from ages 18 to 50 years had a multivariate RR (95% CI) of 0.74 (0.45-1.22; P_{trend} = 0.46) compared with participants of stable weight (<3 kg weight gain or loss).

Participants who were physically active between ages 15 and 18 years (at least 51.6 MET-h/wk of vigorous, moderate, and/or light intensity activity) had reduced glioma risk (RR, 0.64; 95% CI, 0.44-0.93; P_{trend} = 0.02) relative to participants who were inactive (≤11.5 MET-h of activity) during these years (Table 5). Participants who were active between ages 19 and 29 years also had reduced glioma risk (RR, 0.65; 95% CI, 0.44-0.94), but the trend was not statistically significant (P_{trend} = 0.17). Physical activity between ages 35 and 39 years and during the past 10 years was unassociated with risk of glioma or glioblastoma.

Discussion

In this large prospective study of men and women ages 50 to 71 years at baseline, adult height and obesity at age 18 years were strongly associated with increased glioma risk, and physical activity at ages 15 to 18 years was associated with decreased glioma risk. BMI or physical activity after age 18 years showed no association with glioma risk, except obesity at age 35 years. It has been theorized that factors related to early development may be of particular importance to glioma risk (12, 13). Our finding that obesity and/or physical inactivity during adolescence but not adulthood were related to glioma risk supports this hypothesis. In addition, although height, BMI, and physical activity each reflect somewhat different aspects of the childhood environment, they are each indicative of nutrition and energy balance. Taken together, our results implicate energy balance–related factors during childhood and/or adolescence in the etiology of adult-onset glioma.

Although our results suggest that early-life energy balance may influence glioma carcinogenesis, it remains possible that early-life

Table 4. RR (95% CI) of glioma in relation to BMI at specific ages

Variable	BMI category (kg/m^2)					P_{trend}
	<18.5	18.5-24.9	25.0-29.9	30.0-34.9	≥35.0	
BMI at age 18 y						
No. cases	26	175	24	11	0	
Age- and sex-adjusted RR (95% CI)	0.75 (0.50-1.13)	1.00 (reference)	1.04 (0.68-1.60)	3.69 (2.01-6.80)	— (—)	0.006
Multivariate RR* (95% CI)	0.69 (0.45-1.05)	1.00 (reference)	1.04 (0.67-1.59)	3.74 (2.03-6.90)	— (—)	0.003
Mutually adjusted† RR (95% CI)	0.68 (0.45-1.03)	1.00 (reference)	1.05 (0.68-1.63)	3.91 (2.08-7.35)	— (—)	0.003
BMI at age 35 y						
No. cases	5	140	73	10	8	
Age- and sex-adjusted RR (95% CI)	0.82 (0.34-2.01)	1.00 (reference)	1.19 (0.89-1.60)	1.05 (0.55-2.01)	3.82 (1.87-7.82)	0.01
Multivariate RR (95% CI)	0.72 (0.29-1.79)	1.00 (reference)	1.19 (0.89-1.60)	1.07 (0.56-2.05)	4.05 (1.97-8.32)	0.01
Mutually adjusted‡ RR (95% CI)	0.80 (0.32-2.00)	1.00 (reference)	1.13 (0.83-1.54)	0.87 (0.43-1.76)	2.89 (1.27-6.56)	0.14
BMI at age 50 y						
No. cases	4	105	94	24	9	
Age- and sex-adjusted RR (95% CI)	0.95 (0.35-2.57)	1.00 (reference)	0.97 (0.73-1.29)	1.09 (0.70-1.71)	1.38 (0.70-2.74)	0.51
Multivariate RR (95% CI)	0.86 (0.31-2.37)	1.00 (reference)	0.99 (0.74-1.31)	1.11 (0.71-1.75)	1.46 (0.73-2.92)	0.41
Mutually adjusted‡ RR (95% CI)	0.90 (0.33-2.47)	1.00 (reference)	0.93 (0.70-1.25)	0.95 (0.59-1.53)	1.08 (0.51-2.25)	0.89
Baseline BMI						
No. cases	4	82	95	46	9	
Age- and sex-adjusted RR (95% CI)	1.85 (0.68-5.06)	1.00 (reference)	0.90 (0.67-1.21)	1.27 (0.89-1.83)	0.71 (0.35-1.41)	0.92
Multivariate RR (95% CI)	1.66 (0.59-4.64)	1.00 (reference)	0.90 (0.67-1.22)	1.29 (0.89-1.86)	0.74 (0.37-1.48)	0.95
Mutually adjusted‡ RR (95% CI)	1.70 (0.61-4.76)	1.00 (reference)	0.86 (0.64-1.17)	1.15 (0.78-1.68)	0.59 (0.29-1.21)	0.47

*Multivariate models are adjusted for age at baseline, age-squared, gender, race (White, Black, other), highest level of education (did not complete high school, completed high school, some college, completed college), and marital status (married, divorced, separated, widowed, unmarried). Models of BMI at age 18 years were additionally adjusted for height at age 18 years (<1.60, 1.60-1.64, 1.65-1.69, 1.70-1.74, 1.75-1.79, 1.80-1.84, 1.85-1.90, ≥1.90 m) and physical activity at age 18 years (≤11.5, 11.6-29.0, 29.1-41.5, 41.6-51.5, ≥51.6 MET-h/wk). Models of BMI at age 35 years were adjusted for physical activity at age 35 to 39 years and adult height. Models of BMI at age 50 years and baseline BMI were adjusted for physical activity during the past 10 years and adult height.

†Additionally adjusted for baseline BMI.

‡Additionally adjusted for BMI at age 18 years.

Table 5. RR (95% CI) of glioma in relation to physical activity level at specific ages

Variable	MET-h/wk of physical activity					P_{trend}
	≤11.5	11.6-29.0	29.1-41.5	41.6-51.5	≥51.6	
Activity between ages 15 and 18 y						
No. cases	50	53	40	50	64	
Age- and sex-adjusted RR (95% CI)	1.00 (reference)	0.96 (0.65-1.41)	0.91 (0.60-1.38)	0.92 (0.62-1.36)	0.67 (0.46-0.97)	0.03
Multivariate* RR (95% CI)	1.00 (reference)	0.93 (0.63-1.37)	0.85 (0.56-1.30)	0.87 (0.59-1.29)	0.64 (0.44-0.93)	0.02
Mutually adjusted† RR (95% CI)	1.00 (reference)	0.93 (0.63-1.37)	0.87 (0.57-1.33)	0.87 (0.58-1.30)	0.64 (0.43-0.94)	0.02
Activity between ages 19 and 29 y						
No. cases	53	51	30	65	58	
Age- and sex-adjusted RR (95% CI)	1.00 (reference)	0.71 (0.49-1.05)	0.73 (0.47-1.15)	0.94 (0.66-1.36)	0.67 (0.46-0.97)	0.21
Multivariate RR (95% CI)	1.00 (reference)	0.69 (0.47-1.02)	0.70 (0.45-1.10)	0.91 (0.63-1.31)	0.65 (0.44-0.94)	0.17
Mutually adjusted‡ RR (95% CI)	1.00 (reference)	0.73 (0.48-1.11)	0.77 (0.46-1.27)	1.12 (0.71-1.77)	0.94 (0.56-1.57)	0.58
Activity between ages 35 and 39 y						
No. cases	53	64	27	62	51	
Age- and sex-adjusted RR (95% CI)	1.00 (reference)	0.85 (0.59-1.23)	0.79 (0.50-1.26)	0.97 (0.67-1.40)	0.79 (0.53-1.16)	0.45
Multivariate RR (95% CI)	1.00 (reference)	0.83 (0.58-1.20)	0.77 (0.48-1.22)	0.94 (0.65-1.36)	0.78 (0.53-1.15)	0.42
Mutually adjusted‡ RR (95% CI)	1.00 (reference)	0.90 (0.62-1.31)	0.85 (0.52-1.38)	1.14 (0.76-1.71)	1.05 (0.67-1.66)	0.49
Activity during the past 10 y						
No. cases	51	77	26	55	48	
Age- and sex-adjusted RR (95% CI)	1.00 (reference)	1.03 (0.72-1.47)	0.83 (0.52-1.33)	0.95 (0.65-1.39)	0.89 (0.60-1.32)	0.43
Multivariate RR (95% CI)	1.00 (reference)	0.99 (0.69-1.41)	0.78 (0.49-1.26)	0.91 (0.62-1.33)	0.86 (0.58-1.28)	0.36
Mutually adjusted‡ RR (95% CI)	1.00 (reference)	1.04 (0.73-1.49)	0.83 (0.51-1.34)	1.01 (0.68-1.50)	1.01 (0.66-1.53)	0.90

*Multivariate models are adjusted for age at baseline, age-squared, gender, race (White, Black, other), highest level of education (did not complete high school, completed high school, some college, completed college), and marital status (married, divorced, separated, widowed, unmarried). Models of physical activity between ages 15 and 18 years were additionally adjusted for height at age 18 years (<1.60, 1.60-1.64, 1.65-1.69, 1.70-1.74, 1.75-1.79, 1.80-1.84, 1.85-1.90, ≥1.90 m) and BMI at age 18 years (<18.5, 18.5-24.9, 25.0-29.9, 30.0-34.9, ≥35.0 kg/m^2). Models of physical activity between ages 19 and 29 years were adjusted for BMI at age 18 years and adult height. Models of physical activity between ages 35 and 39 years were adjusted for BMI at age 35 years and adult height. Models of physical activity during the past 10 years were adjusted for baseline BMI and adult height.
†Additionally adjusted for physical activity during the past 10 years.
‡Additionally adjusted for physical activity during the ages 15 to 18 years.

height, BMI, and physical inactivity each act as proxies for other factors that increase glioma risk. At this time, it is not clear what such factors might be. For example, high socioeconomic status is related to both tallness (14, 15) and increased risk of glioma (4); therefore, the height and glioma relation could theoretically be confounded by socioeconomic status. However, high socioeconomic status is related to low prevalence of childhood/adolescent obesity; therefore, the direction of the confounding would run counter to results that we observed. Thus, unlike with tallness, our adolescent obesity and glioma findings could not be explained by confounding by socioeconomic status. Our study lacked data on many childhood exposures potentially related to energy balance; thus, we were unable to investigate confounding by these factors in detail.

The biological mechanisms by which early-life energy balance could influence glioma risk are speculative. Possibly, height is associated with glioma risk through its association with insulin-like growth factor (IGF) levels during childhood. Childhood levels of IGF-I show a dose-response relation with growth in height (16) and elevated levels have been linked to increased risk of certain cancers (17). IGFs are key players in early brain development with diverse effects on differentiation, proliferation, and apoptosis of brain cells (18). Thus, a biologically plausible link with glioma risk exists. Alternatively, genes that influence linear growth may also be related to glioma susceptibility (discussed in ref. 6), thus explaining the association. Height may also be related to glioma risk because tallness is a marker for a greater number of cells in the body, including in the brain, and this increases the probability of at least one cell undergoing malignant transformation (6).

The association of adolescent BMI and physical activity with glioma risk could be mediated through their association with circulating insulin levels. Hyperinsulinemia is common among obese and sedentary persons and insulin is known to have promitotic properties (19), thereby potentially increasing glioma risk. Insulin, because of its extensive homology with IGF-I, also increases free (unbound) IGF-I through competition for IGF-I binding proteins (20). Thus, although speculative, it is possible that height, BMI, and physical activity are each linked with glioma risk through the shared biological factor of free IGF-I levels. Finally, genes that influence BMI are highly expressed in the brain (21) and could also mediate glioma susceptibility.

Our findings on height and glioma risk are similar to those recently reported for women in the Million Women Study (5). In this study, the authors reported a 24% increased glioma risk per 10 cm increment in height; we report here a 30% increased glioma risk per 10 cm increment among women. Other comparatively small prospective cohort studies relating height to risk of brain and central nervous system tumors (a grouping that includes gliomas as well as other cancers) suggest a positive association (6). Taken together, the totality of available evidence strongly implicates height as a risk factor for glioma.

Our analyses associating BMI and physical activity during adolescence with glioma risk are, to our knowledge, the first data published on adolescent BMI, physical activity, and glioma. Three prospective cohort studies (5, 22, 23) and one case-control study (24) have examined adult BMI in relation to risk of brain and central nervous system tumors but with no evidence of an association. Only one study examined physical activity (during adulthood) in relation to glioma but found no association (5). In our study, the associations between adult BMI, adult physical activity, and glioma risk were also null.

The primary limitation of our study is that our measures of BMI and physical activity during adolescence required participants to recall their weight and physical activity level from many decades in the past. Imprecision in recalled weight and physical activity could potentially result in an attenuation of the magnitude of RRs. Recalled past weight, including over durations of 20 to 66 years, is highly correlated with measured past weight, with correlations ranging from 0.6 to 0.9 (discussed in ref. 25). Therefore, misclassification of weight would be expected to only modestly affect RRs. However, the correlation of recalled physical activity with measured past physical activity is weak (r = 0.30 for 15-year recall in ref. 26), so misclassification of physical activity could affect these RRs. A further limitation is that our findings for BMI at age 18 years are based on relatively modest case numbers (n = 11), as few of our study members were obese at this age. Also, our data do not allow us to distinguish between whether the energy balance and glioma risk associations reflect a possible "beneficial" effect of undernutrition (as may be the case for the link between shortness and low glioma risk) or a deleterious effect of overnutrition (as may be the case for the association between obesity at age 18 years and glioma).

An additional challenge in the modeling of BMI and/or physical activity during adolescence is that adjustment for baseline covariates could, in theory, result in exaggerated associations with glioma (27). This could occur if undiagnosed subclinical glioma influences baseline covariate values. However, in models that adjust for only age and sex, we found results nearly identical to those of the multivariate models. Because neither age nor sex is influenced by subclinical glioma before baseline, it seems unlikely that bias introduced by baseline adjustment is a major contributor to our findings.

Strengths of our study include the prospective design and the availability of data on body weights and physical activity throughout the entire lifespan. In addition, the large cohort size allowed us to examine with precision glioma risk according to narrow categories of height, physical activity, and BMI, thereby enabling assessment of dose-response relationships. Detailed information on possible confounders allowed us to control for important factors such as education and race that may be associated with height, BMI, and/or physical activity.

In summary, our data suggest that energy balance during childhood and/or adolescence may play a role in the etiology of adult-onset glioma. One implication is that biological pathways linking energy balance and cancer risk, particularly levels of IGFs and insulin during childhood, should be more closely investigated as important in glioma etiology. Whether the energy balance and glioma associations are due to a protective effect of early-life undernutrition, a harmful effect of overnutrition, or are due to other energy balance–related factors is uncertain. However, taken together with other evidence linking cancer risk to childhood obesity (28, 29), our results provide preliminary support for the importance of weight maintenance and a physically active lifestyle during childhood and adolescence for reducing glioma risk.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

Received 5/14/09; revised 8/4/09; accepted 8/16/09; published OnlineFirst 10/6/09.

Grant support: Intramural Research Program of the NIH/National Cancer Institute.

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We thank the participants in the NIH-AARP Diet and Health Study for outstanding cooperation.

S.C. Moore had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Cancer incidence data from the Atlanta metropolitan area were collected by the Georgia Center for Cancer Statistics, Department of Epidemiology, Rollins School of Public Health, Emory University. Cancer incidence data from California were collected by the California Department of Health Services, Cancer Surveillance Section. Cancer incidence data from the Detroit metropolitan area were collected by the Michigan Cancer Surveillance Program, Community Health Administration, State of Michigan. The Florida cancer incidence data used in this report were collected by the Florida Cancer Data System under contract to the Department of Health. The views expressed herein are solely those of the authors and do not necessarily reflect those of the contractor or Department of Health. Cancer incidence data from Louisiana were collected by the Louisiana Tumor Registry, Louisiana State University Medical Center in New Orleans. Cancer incidence data from New Jersey were collected by the New Jersey State Cancer Registry, Cancer Epidemiology Services, New Jersey State Department of Health and Senior Services. Cancer incidence data from North Carolina were collected by the North Carolina Central Cancer Registry. Cancer incidence data from Pennsylvania were supplied by the Division of Health Statistics and Research, Pennsylvania Department of Health, Harrisburg, Pennsylvania. The Pennsylvania Department of Health specifically disclaims responsibility for any analyses, interpretations or conclusions.

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