Published by Oxford University Press on behalf of the International Epidemiological Association 2012. *International Journal Of Epidemiology* 2012;**41**:1075–1085
doi:10.1093/ije/dys114

Association between adult height, genetic susceptibility and risk of glioma

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Accepted 19 June 2012

Background Some, but not all, observational studies have suggested that taller stature is associated with a significant increased risk of glioma. In a pooled analysis of observational studies, we investigated the strength and consistency of this association, overall and for major sub-types, and investigated effect modification by genetic susceptibility to the disease.

Methods We standardized and combined individual-level data on 1354 cases and 4734 control subjects from 13 prospective and 2 case–control studies. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) for glioma and glioma sub-types were estimated using logistic regression models stratified by sex and adjusted for birth cohort and study. Pooled ORs were additionally estimated after stratifying the models according to seven recently identified glioma-related genetic variants.

Results Among men, we found a positive association between height and glioma risk (⩾190 vs 170–174 cm, pooled OR = 1.70, 95% CI: 1.11–2.61; *P*-trend = 0.01), which was slightly stronger after restricting to cases with glioblastoma (pooled OR = 1.99, 95% CI: 1.17–3.38; *P*-trend = 0.02). Among women, these associations were less clear (⩾175 vs 160–164 cm, pooled OR for glioma = 1.06, 95% CI: 0.70–1.62; *P*-trend = 0.22; pooled OR for glioblastoma = 1.36, 95% CI: 0.77–2.39; *P*-trend = 0.04). In general, we did not observe evidence of effect modification by glioma-related genotypes on the association between height and glioma risk.

Conclusion An association of taller adult stature with glioma, particularly for men and stronger for glioblastoma, should be investigated further to clarify the role of environmental and genetic determinants of height in the etiology of this disease.

Keywords Height, brain cancer, glioma, cancer, epidemiology

Introduction

Brain and central nervous system (CNS) malignancies occur rarely, with an average annual age-adjusted incidence of 8.9 per 100 000 adults in the USA from 2004 to 2008.[1] Gliomas, which are thought to arise from glial cells, account for ~80% of all primary brain and CNS malignancies and comprise a diverse group of histological sub-types, including various types of astrocytoma (including glioblastoma), oligodendroglioma and ependymal tumours and medulloblastoma, which occur mostly in children. Of these, glioblastoma was the most common (~50%) and most lethal (5-year survival: 4.7%) sub-type diagnosed in the USA between 1995 and 2008.[1]

The aetiology of glioma remains largely unknown, and few of the established risk factors for the disease are modifiable. Incidence of glioma is higher in men compared with women (7.1 vs 5.0 per 100 000 person-years) and increases with age, peaking between the ages of 75 and 84 years.[1] High-dose exposure to ionizing radiation has been associated with an increased risk of glioma, whereas having a history of asthma or other allergic conditions has been associated with reduced risk.[2] In addition, genome-wide association studies have identified a limited number of germline genetic variants associated with glioma risk, including rs11979158/*EGFR*, rs2252586/*EGFR*, rs2736100/*TERT*, rs4295627/*CCDC26*, rs4977756/*CDKN2A-CDKN2B*, rs498872/*PHLDB1* and rs6010620/*RTEL1*.[3–5]

Some,[6–8] but not all,[9–11] epidemiological studies have found that men and women of taller stature have a significant increased risk of glioma. Adult height reflects cumulative effects of numerous low-penetrant genetic variants in addition to a host of early-life hormonal and environmental exposures, including nutritional status, history of illness or psychosocial stress and circulating growth factors.[12–18] Height may also be an indicator for socio-economic status.[18] A positive association between height and glioma risk could be attributable to any one, or a combination, of these factors. However, any influence of height on the development of glioma could be masked among persons with an underlying genetic susceptibility to the disease, particularly if the association for height is relatively weak. Alternatively, some height-related exposures and glioma-related genetic variants may influence glioma development via common biological pathways.

In this analysis, we pooled (i.e. standardized and combined) original data from 13 prospective cohort and 2 case–control studies to examine the association between adult height and risk of glioma, overall and for major sub-types. We also conducted a meta-analysis of these results combined with those from six previously published studies on this topic. To our knowledge, this is both the first pooled analysis and the first meta-analysis on the association between height and risk of glioma and also the first study to evaluate possible effect modification of the association between adult height and glioma risk by glioma-related genotypes.

Methods

Study population

Individual questionnaire and genetic data were contributed by 13 prospective cohort studies [Agricultural Health Study (AHS); Alpha-Tocopherol Beta-Carotene (ATBC) Cancer Prevention Study; CLUE I-II; Cancer Prevention Study II Nutrition Cohort (CPS-II); Melbourne Collaborative Cohort Study (MCCS); Multiethnic Cohort (MEC); Northern Sweden Health and Disease Study (NSHDS); New York University – Women's Health Study (NYUWHS); Physicians' Health Study I and II (PHS); Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial;

Shanghai Men's and Women's Health Study (SMWHS); Vitamins and Lifestyle (VITAL) and Women's Health Study (WHS)] and two case–control studies [National Cancer Institute–Brain Tumor Society adult brain study (NCI–BTS) and National Institute for Occupational Safety and Health Upper Midwest Health Study (NIOSH–UMHS)] participating in the GliomaScan Consortium. Eleven of these studies were conducted in the USA, two in Europe, one in Australia and one in China. Details regarding the design and recruitment for these studies have been described previously.[19–34] After excluding 10 cases and 2 control subjects aged <18 years and 873 cases and 667 control subjects with missing data on baseline height, the final study population consisted of 1354 glioma cases (761 male and 593 female) and 4734 control subjects (3147 male and 1587 female). A brief description of subjects from across the 15 studies participating in GliomaScan, as well as study-specific methods for the selection of control subjects, is shown in Table 1.

Outcome assessment

Glioma cases were generally defined as primary brain tumours with International Classification of Diseases (ICD)-O-3 histology codes 9380–9480, although definitions varied slightly from study to study because of differences in coding schemes and geographical location. We further classified the following sub-groups of glioma according to tumour histology: glioblastoma (ICD-O-3 codes 9440–9442) and oligodendroglioma/oligoastrocytoma (ICD-O-3 codes 9382, 9450, 9451 and 9460).

Questionnaire data

All variables included in this analysis were formatted similarly across studies using standardized definitions and categories. Demographic characteristics, including dates of birth, sex, race/ethnicity (White, Black, American Indian/Alaskan Native, Asian/Pacific Islander, other), education (less than high school graduate, high school graduate or equivalent, some college or vocational school post-high school, college graduate or post-graduate), were self-reported in study-specific questionnaires and were provided by all 15 studies. Height and weight were measured by study personnel in the ATBC, MCCS and SMWHS studies and self-reported in all other studies. Where necessary, height was converted to centimetres (cm) and weight was converted to kilograms (kg). Data on medical history of allergies (yes, no), hormone replacement therapy (ever, never) and smoking (never, former, current) were provided by five of the studies: AHS, ATBC, NCI–BTS, NIOSH–UMHS and PLCO. Missing data were handled by including a missing indicator variable in the models.

Genotyping

Subjects in the 15 studies included here provided blood, saliva or buccal samples, which were used to extract DNA for genotyping. Genotyping was performed using the Illumina 660-W Human BeadChip (San Diego, CA, USA) for all glioma cases. Genotyping for control subjects was conducted using various platforms (see Table 1). To account for differences in the assays used, single nucleotide polymorphism (SNP) data for the control samples were imputed if necessary, as described by Marchini *et al*.[35] Seven genetic variants associated with glioma risk were identified from previous genome-wide association study (GWAS) (rs11979158, rs2252586, rs2736100, rs4295627, rs4977756, rs498872 and rs6010620).[3–5] SNP genotypes were categorized as having 0, 1 or 2 risk alleles, with the risk allele defined as the allele associated with increased risk of glioma. For each subject, we calculated a genetic susceptibility risk score by summing the number of risk alleles (up to two per SNP) across all seven SNPs, with the highest possible score being 14 and the lowest being 0.

Statistical analysis

We investigated the study-specific odds ratios (ORs) and 95% confidence intervals (CIs) for glioma using logistic regression models stratified by sex. All models were adjusted for birth year (<1930, 1930–39, 1940–49, 1950–59, ⩾1960) to account for secular trends in height and height-related exposures, although results did not change substantially after this adjustment. Because additional adjustment for other potential confounders, including race, education, body mass index (BMI) (weight in kilograms divided by height in metres squared), smoking status, hormone replacement therapy use and history of allergies, did not materially change the risk estimates for studies that provided these data, these covariates were not retained in the final adjusted models. The lack of a confounding effect due to race in these models was not surprising, as >97% of the subjects included in studies other than SMWHS were classified as White; stratifying according to study essentially served to control for race in this analysis. The lack of confounding due to BMI was also expected, given that the relationship between height and BMI was very weak (among control subjects, Spearman rho for men = −0.03 and for women = −0.10). Height was modelled both categorically (using 5-cm categories) and continuously (per 5-cm increase). Because we observed a slight increased risk in the lowest-height categories, the next-to-lowest category was assigned as the reference group for both men and women.

A two-step approach was used to combine the data from the 15 studies. For the first step, heterogeneity across the study-specific estimates was tested using the I^2-statistic. Because we did not observe significant heterogeneity across studies, random-effects meta-analysis was used to calculate weighted

Table 1 Descriptive characteristics of the 15 studies participating in GliomaScan and included in the pooled analysis of height and glioma risk

Study	Study acronym	Study type	Control selection	Platform used for genotyping among controls	Study period (recruitment)	Location	Cases	Controls	Mean age at diagnosis, cases (years)	Height in men, median (IQR)	Height in women, median (IQR)
Agricultural Health Study[21]	AHS	Cohort	Frequency-matched 2:1 by year of birth, sex and race	Illumina 660 W	1993–97	USA (IA, NC)	15	33	59	178 (173–185)	165 (157–170)
Alpha-Tocopherol Beta-Carotene Cancer Prevention Study[22]	ATBC	Cohort	Glioma-free control subjects with previous GWAS data	Illumina 610	1985–93	Finland	39	1271	69	174 (169–178)	163 (157–168)
CLUE I: Campaign against cancer and stroke; CLUE II: Cancer and heart disease[23]	CLUE	Cohort	Glioma-free control subjects with previous GWAS data	Illumina 550 K	1974–89	USA (MD)	39	71	65	175 (173–180)	163 (157–168)
Cancer Prevention Study II Nutrition Cohort[24]	CPS-II	Cohort	Glioma-free control subjects with previous GWAS data	Illumina 550 K	1992	USA (21 states)	67	98	73	180 (175–183)	163 (160–168)
Melbourne Collaborative Cohort Study[25]	MCCS	Cohort	Glioma-free control subjects with previous GWAS data	Illumina 550 K	1990–94	Australia	42	83	68	173 (169–177)	160 (155–165)
Multiethnic Cohort[24]	MEC	Cohort	Matched on age, sex and race	Illumina 550 K	1993	USA	4	8	69	175 (173–180)	168 (168–170)
National Cancer Institute–Brain Tumor Society adult brain study[19]	NCI–BTS	Case–control	Frequency-matched 2:1 by hospital, age, sex, race and residential distance from hospital	Illumina 660 W	1994–98	USA (AZ, MA, PA)	389	483	51	180 (178–186)	168 (163–173)
National Institute for Occupational Safety and Health Upper Midwest Health Study[20]	NIOSH–UMHS	Case–control	Population-based control subjects frequency-matched 1.5:1 by age, sex and state	Illumina 660 W	1995–97	USA (IA, MI, MN, WI)	327	581	48	178 (175–183)	165 (160–168)
Northern Sweden Health and Disease Study[27]	NSHDS	Cohort	Matched on age, sex and race	Illumina 660 K	1985–ongoing	Northern Sweden	104	944	52	177 (173–182)	163 (159–167)
New York University – Women's Health Study[28]	NYUWHS	Cohort	Glioma-free control subjects with previous GWAS data	Illumina 550 K	1985–91	USA (NY)	6	13	65		163 (155–163)
Physicians' Health Study I and II[29]	PHS	Cohort	Glioma-free control subjects with previous GWAS data	Illumina 550 K	1982–84, 1997–2001	USA (several states)	39	54	73	178 (175–183)	
Prostate, Lung, Colorectal and Ovarian cancer screening trial[30]	PLCO	Cohort	Glioma-free control subjects with previous GWAS data	Illumina 550 K	1992–2001	USA (several states)	154	866	71	178 (173–183)	165 (160–168)
Shanghai Men's and Women's Health Study[31,32]	SMWHS	Cohort	Glioma-free control subjects with previous GWAS data	Illumina 550 K	1996–2000 (women), 2001–06 (men)	China (urban communities in Shanghai)	39	79	59	169 (167–173)	156 (152–159)
Vitamins and Lifestyle[33]	VITAL	Cohort	Matched on age, sex, race and time to diagnosis	Illumina 660 W	2000–02	USA (WA)	60	118	69	180 (175–183)	165 (160–168)
Women's Health Study[34]	WHS	Cohort	Glioma-free control subjects with previous GWAS data	Illumina 550 K	1991–2009	USA (several states)	30	32	62		165 (160–170)

summary ORs and corresponding 95% CIs for the association between height and glioma risk in men and women.[36] For the second step, the data were combined into one aggregate dataset to calculate pooled ORs and 95% CIs, and corresponding statistical models were additionally adjusted for study. Models that combined male and female subjects were further adjusted for sex. Significant study-by-exposure interactions were handled by adding cross-product terms to the model; the fit of this model was compared with that of a model without the cross-product term using the likelihood ratio test. Trend tests were conducted by modelling categorical variables as continuous and evaluating the statistical significance of the Wald test for that term.

Because an association between height and glioma risk could be masked among persons with an underlying genetic susceptibility to the disease, particularly if the association for height was relatively weak, we also examined the association between height and glioma risk by seven glioma-related genetic variants in the aggregate dataset. Effect modification of height and genotype on the risk of glioma was assessed by comparing the magnitude of the associations for height and glioma risk by genotype. Tests for interaction were conducted by comparing the fit of a model with an additional cross-product term for height and SNP to a model without this term using the likelihood ratio test.

We also used random-effects meta-analysis to summarize data from previously published studies on height and risk of brain and CNS tumours, or glioma, if reported separately.[6–11] Each of these studies reported a per-unit association of height with brain and CNS tumour (or glioma) risk. For consistency and comparability of the results across the studies, we adjusted the published relative risks (RRs) and 95% CIs, where applicable, so that they corresponded to a per 5-cm increase in height. All statistical analyses were conducted using Stata/SE 11.0 (StataCorp, College Station, TX).

Results

Although the results varied widely across studies, we did not find significant between-study heterogeneity in the results for either men or women. Among men, the PLCO cohort was the only study of the 13 in which a significant association between adult height (continuous, per 5 cm) and risk of glioma was observed (Figure 1). When we summarized the data using random-effects models, the studies showed a borderline-positive association between height and glioma risk (summary OR = 1.05, 95% CI: 0.99–1.13). Among women, none of the study-specific results was significant. The random-effects summary estimate for height and total glioma in women was null (OR = 1.02, 95% CI: 0.94–1.10).

Next we combined data from all studies into one aggregate dataset to estimate pooled ORs for the associations between height, modelled both categorically and continuously, and risk of glioma and glioma sub-types. In men, a positive, but not linear, association between height and risk of glioma was observed (Table 2). Compared with the reference group of 170–174 cm, a non-significant positive association was observed in the lowest category of height (<170 cm, pooled OR = 1.42, 95% CI: 0.98–2.05), whereas a significant positive association was observed in the highest category (⩾190 cm, pooled OR = 1.70, 95% CI: 1.11–2.61). The test for trend for men excluding the lowest-height category was significant (P-trend = 0.01). After restricting the outcome to glioblastoma, the association appeared slightly more linear: the magnitude of the OR in the lowest-height category was attenuated (pooled OR = 1.35), whereas the magnitude of the OR at the highest level increased (pooled OR = 1.99) (Table 2). The positive association between continuous height (per 5 cm) and risk of glioblastoma in men was borderline significant (pooled OR = 1.08, 95% CI: 1.00–1.18). No clear association was observed between height and risk of oligodendroglioma in men (pooled OR per 5 cm = 0.92, 95% CI: 0.78–1.09), although the number of cases was small (n = 85) (Supplementary Table 1, available as Supplementary data at *IJE* online).

The shape of the association between height and glioma risk was less clear in women (Table 2). The studies showed an increased risk in the 170–174-cm category compared with the 160–164-cm reference group (pooled OR = 1.44, 95% CI: 1.05–1.98); however, the association was attenuated in the highest category (⩾175 cm, pooled OR = 1.06). The increased risk in the 170–174-cm category became stronger after restricting to glioblastoma (pooled OR = 1.87, 95% CI: 1.24–2.82), but the association for the highest category was similarly attenuated (pooled OR = 1.36) (Table 2). After excluding the lowest category of height, the test for linear trend was statistically significant (P-trend = 0.04). No association was observed between height and risk of oligodendroglioma (pooled OR per 5 cm = 0.93, 95% CI: 0.78–1.10) (Supplementary Table 1, available as Supplementary data at *IJE* online).

We additionally stratified glioma according to age at diagnosis: <60 years, 60–69 years and ⩾70 years. We found no pattern according to age at diagnosis in men. The associations with height among women were somewhat stronger for those diagnosed at younger compared with older ages (data not shown); however, these results were not significantly different (P = 0.18).

Combining men and women together, the studies showed a positive exposure–response association between height and glioma risk, which was more pronounced for glioblastoma (Table 2). Adults who were

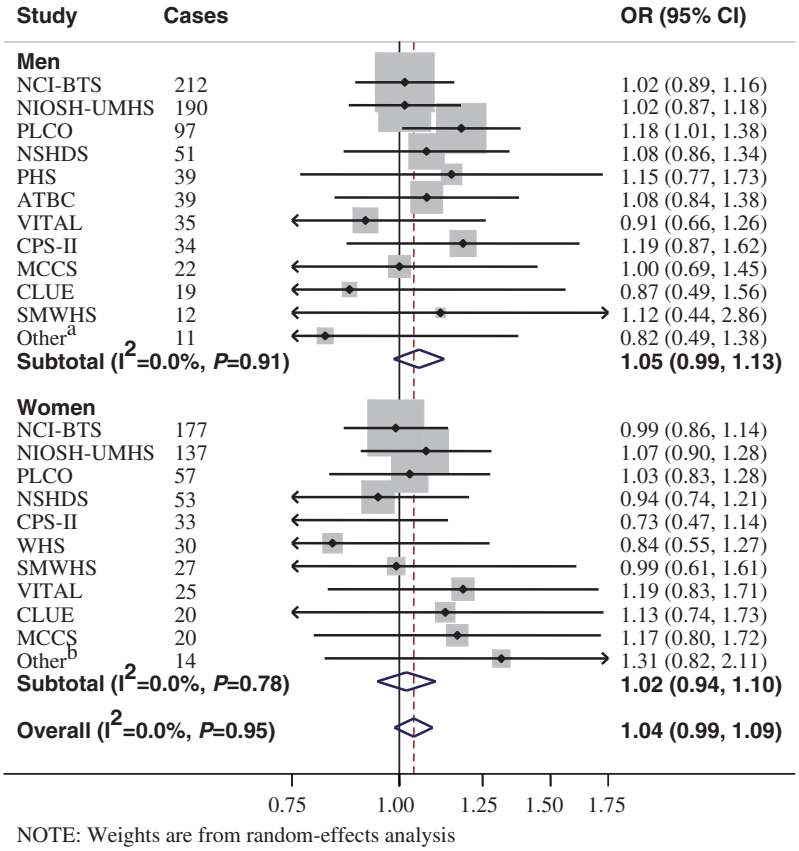

Figure 1 Summary ORs and 95% CIs for glioma risk per 5-cm increase in height. The size of a square reflects the study-specific weight, and the diamond represents the summary OR and 95% CI. The vertical dotted line represents the summary OR. Summary ORs were calculated using random-effects models. Results for studies with <10 cases in men or women are not shown. Analyses were adjusted for year of birth (<1930, 1930–39, 1940–49, 1950–59 and ⩾1960). [a]AHS (n=8 cases) and MEC (n=3 cases); [b]AHS (n=7 cases), MEC (n=1 case) and NYUWHS (n=6 cases)

⩾190 cm in height had an approximate 2-fold increased risk of glioblastoma compared with adults who were between 160 and 169 cm (pooled OR=2.12, 95% CI: 1.26–3.58, P-trend=0.03). Adults who were <160 cm tall did not have a significantly increased risk of glioblastoma (pooled OR=1.13, 95% CI: 0.82–1.55). Overall, the association between height and the risk of glioblastoma appeared to be linear (pooled OR per 5 cm=1.06, 95% CI: 1.00–1.14).

The associations between the seven common genetic variants and risk of glioma and glioblastoma confirm findings from previous GWAS (data not shown).[3–5] We examined the associations between height (<180 vs ⩾180 cm in men and <165 vs ⩾165 cm in women) and risk of glioma stratified by genotype (wild-type vs non-wild-type) (Supplementary Table 2, available as Supplementary data at *IJE* online). In general, we observed no statistically significant interactions between height and the glioma-related genetic variants. Results were similar for glioblastoma (Supplementary Table 3, available as Supplementary data at *IJE* online). The association between height and risk of glioma and glioblastoma was also not modified by genetic susceptibility risk score (data not shown).

We next combined the results from the current analysis with results from six previously published observational studies conducted in the USA, Europe and Asia[6–11] to calculate summary RR estimates for men, women, and men and women combined (Table 3). The summary RRs for a 5-cm increase in height were 1.06 (95% CI: 1.03–1.10) in men, 1.08 (95% CI: 1.04–1.11) in women and 1.07 (95% CI: 1.05–1.09) overall (Figure 2). When we excluded the results from the current analysis, the summary RRs for men and women were similar (RR=1.07 and 1.09, respectively). However, in women, the published data showed a slightly stronger positive association than the summary OR from the current analysis. We observed no statistically significant heterogeneity between studies in either men or women. No consistent patterns emerged by geographical location, study size or outcome definition.

Discussion

Previous studies support a positive, albeit weak, association between height and glioma risk in both men and women.[6–11] We pooled original data from 15 studies,

Table 2 The association between height and glioma risk in men (761 cases/3147 control subjects) and women (593 cases/1587 control subjects)

	Categories of height (in cm)					*P*-trend*	Per 5-cm increase
Men	**<170**	**170–174**	**175–179**	**180–184**	**185–189**	**⩾190**		
Glioma	67	109	196	224	105	60		761
OR (95% CI)[a]	1.42 (0.98–2.05)	1.00 (Ref.)	1.17 (0.88–1.54)	1.50 (1.13–1.98)	1.12 (0.81–1.57)	1.70 (1.11–2.61)	0.01	1.05 (0.98–1.12)
Glioblastoma	31	58	109	115	59	33		405
OR (95% CI)[a]	1.35 (0.82–2.22)	1.00 (Ref.)	1.19 (0.83–1.71)	1.43 (0.99–2.05)	1.19 (0.79–1.82)	1.99 (1.17–3.38)	0.02	1.08 (1.00–1.18)
Women	**<160**	**160–164**	**165–169**	**170–174**	**⩾175**			
Glioma	138	137	153	117	48			593
OR (95% CI)[a]	1.12 (0.83–1.50)	1.00 (Ref.)	1.03 (0.78–1.37)	1.44 (1.05–1.98)	1.06 (0.70–1.62)		0.22	1.02 (0.94–1.10)
Glioblastoma	69	64	86	66	23			308
OR (95% CI)[a]	1.31 (0.89–1.94)	1.00 (Ref.)	1.23 (0.85–1.79)	1.87 (1.24–2.82)	1.36 (0.77–2.39)		0.04	1.04 (0.94–1.16)
Men + women	**<160**	**160–169**	**170–179**	**180–189**	**⩾190**			
Glioma	141	354	459	340	60			1354
OR (95% CI)[b]	1.06 (0.83–1.35)	1.00 (Ref.)	1.04 (0.85–1.27)	1.19 (0.93–1.52)	1.59 (1.05–2.42)		0.04	1.03 (0.98–1.08)
Glioblastoma	71	179	252	178	33			713
OR (95% CI)[b]	1.13 (0.82–1.55)	1.00 (Ref.)	1.20 (0.92–1.57)	1.32 (0.95–1.83)	2.12 (1.26–3.58)		0.03	1.06 (1.00–1.14)

[a]Adjusted for year of birth (<1930, 1930–39, 1940–49, 1950–59, ⩾1960) and study.
[b]Adjusted for year of birth (<1930, 1930–39, 1940–49, 1950–59, ⩾1960), study and sex.
*Calculated by modelling the categorical variable for height as continuous and evaluating the statistical significance of the Wald test; values below the reference group excluded.

including 1354 glioma cases, in one of the largest studies conducted on this topic to date. Overall, we found evidence of a non-linear positive association between height and risk of glioma in men, which became more pronounced after restricting the outcome to glioblastoma. We did not find a clear positive association between height and glioma in women.

Tall stature has been associated with an increased risk of numerous other cancers, including prostate, breast, endometrial, ovarian, colorectal, kidney and thyroid cancers, as well as malignant melanoma, non-Hodgkin lymphoma and leukaemia.[9,37–39] However, the specific biological mechanisms underlying the association between height and increased risk of cancer, including glioma, remain undefined. Increases in the distribution of height during childhood and adulthood with successive birth cohorts are thought to be, at least partly, attributable to secular trends in early-life exposures.[40] In our study, adjustment for birth cohort, which may be an indicator for some of these exposures, did not substantially change the RR estimates. Our results also did not substantially change after adjusting for socio-economic indicators, including race and education, or early medical history of allergies, all of which may be related to height.[18] We found stronger positive associations between height and glioma risk in men compared with women. Taller adolescents and adults, particularly males, have greater circulating levels of insulin-like growth factor (IGF)-I.[41,42] Although involved in regulation of growth during puberty, IGF-I is also thought to play an important role in carcinogenesis, having mitogenetic, anti-apoptotic and pro-angiogenic properties.[43] In a cohort of male smokers, however, lower serum levels of IGF-I were associated with an increased risk of glioma[44]; this observation may explain the slight increased risk of glioma among the shortest men in our study but not the positive association observed in the tallest categories. The generally weaker associations observed in women compared with men in our study may additionally be explained by the narrower range of height or greater potential for height loss with increasing age in women compared with men.[45]

In general, the association we observed between height and glioma risk was not modified by known glioma-related genetic variants. We also did not find that genetic susceptibility to glioma, assessed using a genetic risk score, modified the association between height and glioma or glioblastoma risk in either men or women. Nonetheless, despite the inclusion of a relatively large number of glioma cases, there was limited power to detect significant interactions between height and glioma-related genotypes in this study. Also, the genetic variants examined in the current study were based on results from GWAS and likely reflect incomplete identification of key genetic determinants.

Combining data from multiple studies can allow for greater statistical power to detect relatively weak

Table 3 Description of previous publications on the association between height and risk of glioma

First author	Publication year	Study design	Geographical location	Outcome definition	Number of cases
Helseth	1989	Nested case–control study	Norway	Incident malignant neoplasms and benign tumours of the CNS	Men: 1538; Women: 1511
Moore	2009	Prospective cohort study	USA	Incident glioma: ICD-10 C710–719; ICD-O-3 9380–9480	Men: 341; Women: 139
Sung	2009	Prospective cohort study	South Korea	Incident CNS cancers: ICD-10 C70–C72	Men: 282; Women: 866
Batty	2010	Pooled analysis of prospective cohort studies	Asia Pacific region	Brain and CNS (mortality only): ICD-9 191–192 or ICD-10 C70–72	Men: 141; Women: 57
Benson	2008	Prospective cohort study	UK	Incident glioma: ICD-10 C70, 71, 72.0, 75.1–3, D32, D33, D35.2–4, D42, D44.3–5; ICD-O-3 9380–9481	Women: 646
Michaud	2011	Prospective cohort study	Europe	Incident glioma: ICD-O-2 9380–9460, 9505	Men: 167; Women: 173

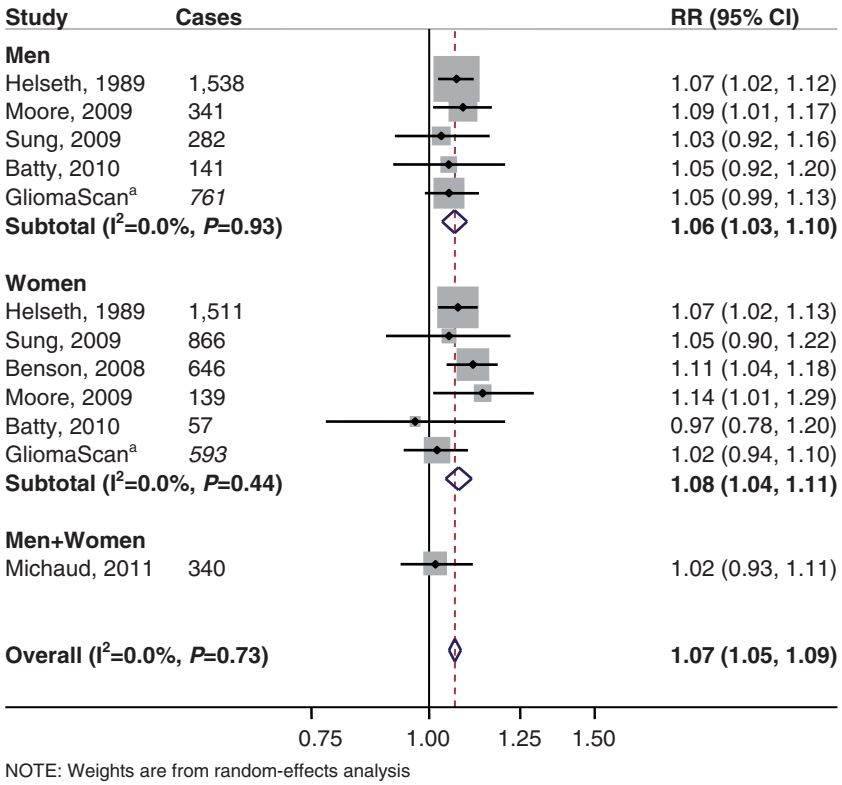

Figure 2 Summary RRs and 95% CIs for brain and CNS tumour (or glioma, if reported separately) risk per 5-cm increase in height. The size of a square reflects the study-specific weight, and the diamond represents the summary RR and 95% CI. The vertical dotted line represents the summary RR. Summary RRs were calculated using random-effects models.
[a]Summary OR and 95% CI from the current analysis, as shown in Figure 1

associations than can be obtained from an individual study alone. By combining data across 15 observational studies for the current analysis, we accrued a relatively large number of cases that allowed for a relatively precise examination of the association of height and the risks of glioma sub-types, specifically glioblastoma and oligodendroglioma, although the number of cases in the latter category was still relatively small. Having original data from multiple studies also allowed us to evaluate the consistency of our results by comparing the magnitude and strength of the association by study while using a standard analytic approach.

We had to rely on self-reported measures of height from many of the included studies, which introduced the potential for some misclassification. Errors in self-reported height likely are small in young and middle-aged adults,[46] but over-reporting of height occurs among older adults, in part because height tends to decrease with age.[45,46] In fact, we found that the positive association for height in women was stronger among cases diagnosed at younger vs older ages. We lacked information on leg length, which is more sensitive to early-life environmental influences compared with trunk length[13] and may be a stronger determinant of future chronic disease outcomes, including coronary heart disease.[47] Data on some potential confounding factors, such as history of allergies, were only available for some of the included studies; however, additional adjustment for these factors did not change the associations observed in those studies.

The body of evidence suggests that taller men, and possibly taller women, have an increased risk of glioma, although, for women, the association observed in the current analysis was weaker than that reported in previous publications.[6–11] In the current analysis, the associations for both men and women were more pronounced for glioblastoma, the most common sub-type of glioma. The responsible mechanisms underlying the association between height and glioma risk are not certain, as adult stature reflects a complex combination of early-life exposures, socio-economic factors, long-term effects of circulating growth factors and genetic variation, some or all of which may be involved in the development of glioma. Considering the paucity of established risk factors, future studies investigating the role of environmental and genetic determinants of height with risk of glioma may provide some insight into the aetiology of this poorly understood disease.

Supplementary Data

Supplementary Data are available at *IJE* online.

Funding

This work was supported in part by the Intramural Research Program of the NCI, National Institutes of Health.

Acknowledgements

The authors thank all investigators who have contributed data for the GliomaScan study.

For CPS-II Nutrition Cohort: The Cancer Prevention Studies are supported by the American Cancer Society. Efforts of the ACS the study management group to maintain and follow the cohort are acknowledged. ACS investigators also acknowledge the contributions from central cancer registries supported through the Centers for Disease Control and Prevention's National Program of Cancer Registries and cancer registries supported by the National Cancer Institute's Surveillance Epidemiology and End Results Program.

For NYUWHS: The NYUWHS is supported by National Cancer Institute grants R01 CA098661 and P30 CA016087 and by Center grant ES000260 from the National Institute of Environmental Health Sciences.

For PHS: The PHS is supported by grants CA 97193, CA 34944, CA 40360, HL 26490, and HL 34595 from the National Institutes of Health.

For CLUE: Cancer incidence data were provided by the Maryland Cancer Registry, Center for Cancer Surveillance and Control, Department of Health and Mental Hygiene, 201 W. Preston Street, Room 400, Baltimore, MD 21201, USA; www.fha.state.md.us/cancer/registry/, 410-767-4055. The authors acknowledge the State of Maryland, the Maryland Cigarette Restitution Fund and the National Program of Cancer Registries of the Centers for Disease Control and Prevention for the funds that support the collection and availability of the cancer registry data. The findings and conclusions of this report are those of the authors and do not necessarily represent the views of the Maryland Cancer Registry.

For PLCO: This research was supported by the Intramural Research Program of the Division of Cancer Epidemiology and Genetics and by contracts from the Division of Cancer Prevention, NCI, National Institutes of Health (NIH) and Department of Health and Human Services (DHHS). The authors thank Drs Christine Berg and Philip Prorok, Division of Cancer Prevention, NCI, the Screening Center investigators and staff of the PLCO cancer screening trial, Mr Tom Riley and staff, Information Management Services, Inc., Ms Barbara O'Brien and staff, Westat, Inc., Mr Tim Sheehy and staff, DNA Extraction and Staging Laboratory, SAIC-Frederick, Inc. and Ms Jackie King and staff, BioReliance, Inc.

For NIOSH: The contributions of former laboratory director Mary Ann Butler are gratefully acknowledged. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the NIOSH.

For MCCS: Infrastructure support for the MCCS recruitment and follow-up is provided by the Cancer Council Victoria, and cohort recruitment was partly funded by VicHealth. This work using the MCCS was supported by the Australian National Health and Medical Research Council (grant numbers 209057, 251533 and 396414).

For VITAL: Grant K05CA154337 is funded by the NCI and the NIH Office of Dietary Supplements (ODS).

Conflict of interest: None declared.

KEY MESSAGES

- Findings from this and previous studies suggest that taller men, and possibly taller women, have an increased risk of glioma. However, for women, the association observed in the current study was weaker than that reported in most previous studies. In the current study, the associations for both men and women were more pronounced for glioblastoma, the most common sub-type of glioma.

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