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ORIGINAL ARTICLE

Overweight, obesity and height as risk factors for meningioma, glioma, pituitary adenoma and nerve sheath tumor: a large population-based prospective cohort study

Markus K. H. Wiedmann[a,b,c], Cathrine Brunborg[d], Antonio Di Ieva[b], Kristina Lindemann[c,e], Tom B. Johannesen[f], Lars Vatten[g], Eirik Helseth[a,c] and John A. Zwart[c,h]

[a]Department of Neurosurgery, Oslo University Hospital, Ulleval, Oslo, Norway; [b]Neurosurgery Unit, Faculty of Medicine and Health Sciences, Macquarie University, Sydney, NSW, 2109, Australia; [c]Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway; [d]Oslo Centre for Biostatistics and Epidemiology, Research Support Services, Oslo University Hospital, Oslo, Norway; [e]Department of Gynecologic Oncology, Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway; [f]The Cancer Registry of Norway, Oslo, Norway; [g]Department of Public Health, Norwegian University of Science and Technology, Trondheim, Norway; [h]FORMI and Department of Neurology, Oslo University Hospital, Ulleval, Oslo, Norway

ABSTRACT

Background: In 2016, the International Agency for Research on Cancer (IARC) has announced that avoiding body fatness (i.e. overweight and obesity) contributes to prevent meningioma occurrence, but considered the available evidence for glioma inadequate. The association of body fatness with other CNS tumor subgroups is largely unknown.

Objectives: To assess whether body fatness or body height are associated with risk for meningioma, glioma, pituitary adenoma (PA) or nerve sheath tumor (NST) in a large population-based Norwegian cohort.

Methods: In this prospective cohort study of 1.8 million Norwegian residents, weight and height were measured at baseline and incident intracranial tumors were subsequently identified by linkage to the Cancer Registry of Norway. Cox regression analyses were performed to estimate risk for each tumor subgroup in relation to anthropometric measures, stratified by sex and in different age groups.

Results: During 54 million person-years of follow-up 3335 meningiomas, 4382 gliomas, 1071 PAs and 759 NSTs were diagnosed. Obesity (BMI $\geq$30 kg/m^2) was not associated with risk for meningioma or glioma, but was significantly associated with risk for PA (HR 1.43; 95% CI 1.09–1.88) compared with the reference group (BMI 20–24.9 kg/m^2). For intracranial NSTs, obesity was associated with reduced tumor risk (HR 0.68; 95% CI 0.46–0.99). Body height was associated with increased risk for all four tumor subgroups.

Conclusions: This study does not confirm overweight or obesity as risk factors for meningioma. Additionally, overweight and obesity can be quite confidently excluded as risk factors for glioma. However, this study indicates that body fatness increases the risk for PA, while it reduces the risk for NST.

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Introduction

According to the World Health Organization (WHO), disease prevention is the most cost-effective long-term strategy for cancer control. Over a decade ago, the International Agency for Research on Cancer (IARC) has concluded that there is substantial evidence for the avoidance of body fatness (i.e. overweight and obesity) to prevent cancer of colon, breast (in postmenopausal women), endometrium, kidney (renal cell carcinoma) and adenocarcinoma of the esophagus [1]. In 2016, the IARC announced an additional eight cancers for which sufficient evidence suggested that the absence of body fatness lowered cancer risk. For the first time, this included a tumor of the central nervous system (CNS), meningioma [2]. However, the evidence of an association between body mass index (BMI) and risk for the most common malignant tumor of the CNS, glioma, was considered inadequate [2].

Epidemiological studies on intracranial tumors commonly called *brain tumors* are challenging due to the low incidence and heterogeneity of different brain tumor subgroups, which share the anatomic location in and around the brain, but differ largely in histogenesis and behavior. Therefore, subgroups of brain tumors should be considered separately in epidemiologic studies. However, to assess potential risk factors for tumor subgroups with low incidence, this requires cohort studies with large numbers of study participants and long follow-up, not only to identify risk factors, but also to have sufficient power to exclude factors that are not associated

CONTACT Markus K. H. Wiedmann markus.kh.wiedmann@gmail.com Department of Neurosurgery, Oslo University Hospital, P.O. Box 4950 Nydalen, 0424 Oslo, Norway

Supplemental data for this article can be accessed here.

with tumor risk. This explains why the large majority of epidemiological studies on brain tumors have predominantly assessed risk factors for meningioma and glioma, the two largest brain tumor subgroups, whereas evidence for other brain tumor subgroups is scarce.

For meningioma, several recent systematic reviews and meta-analyses have reported a positive association between overweight and obesity and meningioma risk [3–5], while the association of BMI with other brain tumor subgroups remains unclear [6–16].

The objective of this study was to assess whether overweight, obesity or body height are associated with the four most common brain tumor subgroups of meningioma, glioma, pituitary adenoma and nerve sheath tumor in a large population-based cohort of Norwegian residents, both overall and in stratified analyses for sex and different age groups.

Methods

This study cohort consists of men and women between 14 and 80 years of age who participated in the last national screening campaign for tuberculosis in Norway, performed by the National Mass Radiography Service between 1963 and 1975. The program was carried out in 17 of the 19 Norwegian counties and had an attendance rate of 83% [6]. Trained personnel measured body height and weight of study participants at baseline (the time of inclusion into the study). Subsequent intracranial tumors were identified by linkage to the Cancer Registry of Norway using the unique personal identification number allocated to each Norwegian resident.

The diagnosis of intracranial tumors was based on the International Classification of Diseases for Oncology, third edition (ICD-O-3) and the International Classification of Diseases, 7th Revision (ICD-7) morphology and topography codes. Intracranial location was defined by ICD-7 codes 193.0–193.2 and 195.3–195.5. Histopathological tumor subgroups were defined as follows: ICD-O-3 morphology code 9530-9539 for meningioma, 9380-9384 and 9391-9460 for glioma, 8140-8300 for PA and 9540-9570 for NST.

BMI was calculated as weight divided by height squared (kg/m^2) and categorized as <20, 20–24.9, 25–29.9 and $\geq$30 kg/m^2. Overweight was defined as BMI 25–29.9 kg/m^2, obesity as BMI $\geq$30 kg/m^2, underweight as BMI <20 kg/m^2, while BMI 20–24.9 kg/m^2 was used as the reference category. Associations were also assessed per 5 kg/m^2 increase in BMI. Birth year was categorized into four cohorts: $<$1911, 1911–1925, 1926–1941 and $>$1941. Age was categorized as $<$30, 30–44, 45–59 and $\geq$60 years of age. Body height was categorized as quartiles for men and women, and per 10 cm increase in height.

This study was approved by the Regional Committee for Ethics in Medical and Health Care Research and by the Norwegian Data Inspectorate.

Statistical analysis

Follow-up time was calculated as person-years from study baseline until the date of primary intracranial tumor diagnosis or any other cancer diagnosis, date of emigration, death from any cause, or to the end of follow-up at 15 December 2011, whichever occurred first.

Cox proportional hazard regression, using attained age as the time axis and adjusting for birth cohort and sex, was performed to calculate hazard ratios (HRs) with 95% confidence intervals (CIs). The likelihood of reverse causality was tested in sensitivity analysis by excluding participants with 5 or less years of follow-up. Stratified analyses were performed for sex and different age groups. The proportional hazard assumptions were tested by plotting the logarithm of the integrated hazards (log-log survival plots) and by Schoenfeld tests, and found to be satisfied. The difference between HR estimates was assessed as described by Altman and Bland (test of interaction) [17]. Analyses were performed with STATA/SE statistics software Version 14.0 (StataCorp, 4905 Lakeway Dr, TX 77845, USA), using two-sided probability with a significance level of .05.

Results

In this study, 1,855,333 participants were followed for a median period of 33.4 years (inter quartile range: 18.7–41.5). Table 1 shows the baseline characteristics of the study cohort. During follow-up 3335 meningiomas, 4382 gliomas, 1071 PAs, and 759 NSTs were identified.

There was no association of overweight or obesity with meningioma risk in the total population, or in separate analyses for men and women or different subgroups of age (Table 2 and Supplementary Table S1). However, there was a borderline association of BMI per 5 kg/m^2 increase with risk for meningioma in the total population (HR 1.05; 95% CI 1.00–1.10), which seemed more driven by men (HR 1.13; 95% CI 1.01–1.27), than women (HR 1.05; 95% CI 1.00–1.11) (Table 2). Additionally, the association between BMI per 5 kg/m^2 increase and meningioma risk was found to be significant in the youngest age group $<$30 years (HR 1.12; 95% CI 1.02–1.24) (Supplementary Table S1).

Overweight and obesity or BMI per 5 kg/m^2 increase were not associated with risk for glioma in the overall model, or in

Table 1. Baseline characteristics of the study cohort, including men and women from 14 to 80 years of age.

	Population at risk	Glioma	Meningioma	Pituitary adenoma	Nerve sheath tumor
No of participants	1,855,333	4382	3335	1071	759
Women; No (%)	959,798 (52)	1917 (44)	2452 (74)	473 (44)	417 (55)
Number of participants per age category (in years); No (%)					
14 to 29	510,583 (28)	1295 (30)	963 (29)	478 (45)	334 (44)
30 to 44	438,897 (24)	1581 (36)	1313 (40)	386 (36)	271 (36)
45 to 59	505,836 (27)	1264 (29)	952 (29)	179 (17)	146 (19)
60 to 80	400,017 (22)	242 (6)	107 (3)	28 (3)	8 (1)
BMI categories (in kg/m^2); No (%)					
$<$20	181,140 (10)	385 (9)	302 (9)	129 (12)	93 (12)
20–24.9	934,796 (50)	2444 (56)	1782 (54)	551 (52)	465 (61)
25–29.9	573,754 (31)	1292 (29)	981 (30)	328 (31)	172 (23)
$\geq$30	165,643 (9)	261 (6)	270 (8)	63 (6)	29 (4)
Mean height at baseline measurement; cm (SD)					
Men	175 (7)	176 (7)	176 (7)	177 (7)	176 (7)
Women	162 (6)	164 (6)	163 (6)	165 (6)	164 (6)

SD: standard deviation.

Table 2. HR (95% CIs) for BMI, height and meningioma risk.

Total population				
Meningioma (No)	3355			
Time at risk (years)	54,894,356			
BMI category	<20	20–24.9	25–29.9	≥30
	0.96 (0.84–1.08)	Ref	1.08 (0.99–1.17)	1.12 (0.98–1.27)
BMI per 5 Kg/m^2 increase	1.05 (1.00–1.10)	$p = .04$		
Height per 10 cm increase	1.15 (1.08–1.22)	$p < .001$		
Men				
Meningioma (No)	883			
Time at risk (years)	25,315,486			
BMI category	<20	20–24.9	25–29.9	≥30
	0.89 (0.66–1.21)	Ref	1.14 (0.98–1.32)	1.26 (0.89–1.76)
BMI per 5 Kg/m^2 increase	1.13 (1.01–1.27)	$p = .03$		
Height in Quartiles	1.	2.	3.	4.
	Ref	1.11 (0.90–1.35)	1.23 (1.00–1.51)	1.32 (1.08–1.61)
Height per 10 cm increase	1.16 (1.05–1.28)	$p = .005$		
Women				
Meningioma (No)	2452			
Time at risk (years)	29,578,870			
BMI category	<20	20–24.9	25–29.9	≥30
	0.95 (0.83–1.10)	Ref	1.06 (0.96–1.17)	1.13 (0.98–1.31)
BMI per 5 Kg/m^2 increase	1.05 (1.00–1.11)	$p = .06$		
Height in Quartiles	1.	2.	3.	4.
	Ref	1.12 (0.99–1.27)	1.21 (1.08–1.37)	1.25 (1.11–1.41)
Height per 10 cm increase	1.14 (1.06–1.22)	$p < .001$		

Cox regression analysis with age as the time axis, multivariable for sex (where not stratified), height, BMI and birth year cohort; HR: hazard ratio; Cis: confidence intervals; Ref: reference category.

Table 3. HR (95% CIs) for BMI, height and glioma risk.

Total population				
Glioma (No)	4382			
Time at risk (years)	54,897,197			
BMI category	<20	20–24.9	25–29.9	≥30
	0.97 (0.87–1.09)	Ref	0.98 (0.92–1.05)	0.95 (0.83–1.08)
BMI per 5 Kg/m^2 increase	0.99 (0.94–1.03)	$p = .6$		
Height per 10 cm increase	1.22 (1.17–1.28)	$p < .001$		
Men				
Glioma (No)	2456			
Time at risk (years)	25,345,361			
BMI category	<20	20–24.9	25–29.9	≥30
	1.02 (0.87–1.20)	Ref	1.04 (0.95–1.14)	1.01 (0.82–1.26)
BMI per 5 Kg/m^2 increase	1.03 (0.96–1.10)	$p = .7$		
Height in Quartiles	1.	2.	3.	4.
	Ref	1.28 (1.13–1.45)	1.33 (1.17–1.51)	1.43 (1.26–1.61)
Height per 10 cm increase	1.21 (1.14–1.28)	$p < .001$		
Women				
Glioma (No)	1917			
Time at risk (years)	29,551,836			
BMI category	<20	20–24.9	25–29.9	≥30
	0.92 (0.79–1.07)	Ref	0.91 (0.81–1.01)	0.90 (0.76–1.06)
BMI per 5 Kg/m^2 increase	0.97 (0.91–1.03)	$p = .3$		
Height in Quartiles	1.	2.	3.	4.
	Ref	1.06 (0.92–1.21)	1.18 (1.03–1.35)	1.33 (1.17–1.52)
Height per 10 cm increase	1.25 (1.15–1.35)	$p < .001$		

Cox regression analysis with age as the time axis, multivariable for sex (where not stratified), height, BMI and birth year cohort; HR: hazard ratio; Cis: confidence intervals; Ref: reference category.

subgroup analyses of different age groups or by sex (Table 3 and Supplementary Table S2).

The risk for PA was positively associated with overweight (HR 1.39; 95% CI 1.21–1.61) and obesity (HR 1.43; 95% CI 1.09–1.88) compared with the reference (BMI 20–24.9 kg/m^2) (Table 4). Assessed per 5 kg/m^2 increase in BMI, the risk increase was 16% in the total population, with no significant difference between men and women (Table 4). The association between overweight and obesity and PA risk seemed consistent in different subgroups of age, although the risk estimates were more imprecise and the number of cases too small in the age group 60–80 years for reliable estimates (Supplementary Table S3).

Overweight and obesity were negatively associated with risk for NST in the total population (Table 5). For obesity, NST risk was 32% lower (HR 0.68; 95% CI 0.46–0.99) compared with the reference (BMI 20–24.9 kg/m^2), and there was a 12% risk reduction per 5 kg/m^2 increase in BMI (HR 0.88; 95% CI 0.79–0.99). Interaction analysis did not show any difference between obese men and women (HR 0.64; 95% CI 0.28–1.44

Table 4. HR (95% CIs) for BMI, height and pituitary adenoma risk.

Total population				
Pituitary adenoma (No)	1071			
Time at risk (years)	54,827,536			
BMI category	<20	20–24.9	25–29.9	≥ 30
	1.18 (0.97–1.43)	Ref	1.39 (1.21–1.61)	1.43 (1.09–1.88)
BMI per 5 Kg/m^2 increase	1.16 (1.06–1.27)	$p = .001$		
Height per 10 cm	1.29 (1.17–1.42)	$p < .001$		
Men				
Pituitary adenoma (No)	598			
Time at risk (years)	25,307,001			
BMI category	<20	20–24.9	25–29.9	≥ 30
	1.57 (1.19–2.09)	Ref	1.61 (1.35–1.93)	1.66 (1.09–2.53)
BMI per 5 Kg/m^2 increase	1.29 (1.12–1.47)	$p < .001$		
Height in Quartiles	1.	2.	3.	4.
	Ref	1.37 (1.06–1.78)	1.37 (1.05–1.80)	1.69 (1.32–2.17)
Height per 10 cm increase	1.24 (1.09–1.40)	$p = .001$		
Women				
Pituitary adenoma (No)	473			
Time at risk (years)	29,520,535			
BMI category	<20	20–24.9	25–29.9	≥ 30
	0.86 (0.65–1.14)	Ref	1.12 (0.88–1.41)	1.38 (0.97–1.97)
BMI per 5 Kg/m^2 increase	1.13 (1.00–1.28)	$p = .06$		
Height in Quartiles	1.	2.	3.	4.
	Ref	1.31 (0.97–1.76)	1.18 (0.88–1.60)	1.55 (1.17–2.06)
Height per 10 cm increase	1.34 (1.15–1.58)	$p < .001$		

Cox regression analysis with age as the time axis, multivariable for sex (where not stratified), height, BMI and birth year cohort; HR: hazard ratio; Cis: confidence intervals; Ref: reference category.

Table 5. HR (95% CIs) for BMI, height and intracranial nerve sheath tumor risk.

Total population				
NST (No)	759			
Time at risk (years)	54,819,915			
BMI category	<20	20–24.9	25–29.9	≥30
	1.00 (0.80–1.26)	Ref	0.84 (0.70–1.01)	0.68 (0.46–0.99)
BMI per 5 Kg/m^2 increase	0.88 (0.79–0.99)	$p < .029$		
Height per 10 cm increase	1.16 (1.03–1.30)	$p < .012$		
Men				
NST (No)	342			
Time at risk (years)	25,300,731			
BMI category	<20	20–24.9	25–29.9	≥30
	1.16 (0.81–1.66)	Ref	0.99 (0.77–1.28)	0.64 (0.28–1.44)
BMI per 5 Kg/m^2 increase	0.93 (0.76–1.12)	$p < .44$		
Height in Quartiles	1.	2.	3.	4.
	Ref	1.55 (1.10–2.18)	1.41 (0.99–2.00)	1.34 (0.95–1.88)
Height per 10 cm increase	1.04 (0.89–1.21)	$p < .62$		
Women				
NST (No)	417			
Time at risk	29,519,184			
BMI category	<20	20–24.9	25–29.9	≥30
	0.90 (0.66–1.21)	Ref	0.72 (0.56–0.94)	0.63 (0.41–0.98)
BMI per 5 Kg/m^2 increase	0.85 (0.74–0.99)	0.032		
Height in Quartiles	1.	2.	3.	4.
	Ref	1.16 (0.85–1.59)	1.33 (0.98–1.80)	1.45 (1.07–1.96)
Height per 10 cm increase	1.33 (1.12–1.58)	$p < .001$		

Cox regression analysis with age as the time axis, multivariable for sex (where not stratified), height, BMI and birth year cohort; HR: hazard ratio; Cis: confidence intervals; Ref: reference category.

and HR 0.63; 95% CI 0.41–0.98, respectively; test of interaction: $p = .97$).

In sensitivity analyses, excluding the first five years of follow-up, overweight and obesity were not associated with glioma or meningioma risk, but the association with PA and NST remained unchanged. Furthermore, the weak association between BMI per 5 kg/m^2 increase and risk for meningioma in the overall analysis did not remain significant in sensitivity analysis (HR 1.04; 95% CI 0.99–1.10) (Table 6).

Height was positively and consistently associated with risk for glioma and PA (Tables 3 and 4). The hazard ratio for each 10 cm increase in height in the total population was 1.22 (95% CI 1.16–1.28) for glioma and 1.29 (95% CI 1.17–1.42) for PA. For men in the highest compared to the lowest quartile of height, the risk was 42% higher for glioma and 69% higher for PA; whereas for women, the corresponding risks were 33% for glioma and 55% for PA. These associations were consistent across all age groups (Supplementary Tables S2 and S3).

Height was also positively associated with risk for meningioma and NST (Tables 2 and 5). In the total population, the HR for each 10 cm increase in height was 1.15 (95% CI

Table 6. Men and women; sensitivity analyses (excluding ≤5 years of follow-up); HR (95% CIs) for BMI, height and tumor risk.

Glioma (NO)	4003			
Time at risk (years)	54,650,621			
BMI category	< 20	20–24.9	25–29.9	≥30
	1.00 (0.90–1.12)	Ref	0.96 (0.90–1.04)	0.92 (0.79–1.06)
BMI per 5 Kg/m^2 increase	0.97 (0.92–1.02)	$p = .2$		
Height per 10 cm increase	1.23 (1.17–1.29)	$p < .001$		
Meningioma (NO)	3238			
Time at risk (years)	54,647,938			
BMI category	< 20	20–24.9	25–29.9	≥30
	0.97 (0.85–1.10)	Ref	1.06 (0.98–1.15)	1.10 (0.96–1.26)
BMI per 5 Kg/m^2 increase	1.04 (0.99–1.10)	$p = .09$		
Height per 10 cm increase	1.15 (1.08–1.22)	$p < .001$		
Pituitary adenoma (NO)	1018			
Time at risk (years)	54,581,237			
BMI category	< 20	20–24.9	25–29.9	≥30
	1.21 (1.00–1.48)	Ref	1.36 (1.18–1.58)	1.45 (1.10–1.91)
BMI per 5 Kg/m^2 increase	1.13 (1.03–1.24)	$p = .01$		
Height per 10 cm increase	1.27 (1.15–1.40)	$p < .001$		
Nerve sheath tumor (NO)	729			
Time at risk	54,573,672			
BMI category	< 20	20–24.9	25–29.9	≥30
	1.00 (0.79–1.26)	Ref	0.84 (0.70–1.01)	0.66 (0.44–0.98)
BMI per 5 Kg/m^2 increase	0.86 (0.77–0.97)	$p = .016$		
Height per 10 cm increase	1.16 (1.03–1.30)	$p = .013$		

Cox regression analysis with age as the time axis, multivariable for sex, height, BMI and birth year cohort; HR: hazard ratio; Cis: confidence intervals; Ref: reference category.

1.08–1.22) for meningioma and 1.16 (95% CI 1.03–1.30) for NST. There was a stronger association between height and NST risk in women than in men (HR per 10 cm increase in height: 1.33; 95% CI 1.12–1.58 and HR 1.04; 95% CI 0.89–1.21, test of interaction: $p = .04$).

Discussion

Overweight, obesity and tumor risk

In contrary to our expectations, this study does not contribute to consolidate the previously propagated association between overweight, obesity and risk for meningioma. This differs from the results of three recent meta-analyses, which have reported a positive association between overweight, obesity and meningioma risk [3–5]. However, results of all three meta-analyses were largely based on the same original studies and their methodology requires some consideration: in men, no previous cohort study has demonstrated a significant and consistent association between overweight, obesity and meningioma risk and the positive result in the meta-analyses mainly reflects the results of one case-control study with retrospectively self-reported anthropometric data [18]. In women, the positive association in the meta-analyses was largely influenced by the results of cohort studies that included middle-aged women only, with self-reported baseline data [7,11,12]. In contrary, the EPIC cohort study and the Me-Can project, both European multicentre databases including adult men and women, did not report significant associations between BMI and meningioma risk [9,10]. Our study exceeds the meta-analyses [3–5] in size and power, and we were able to perform subgroup analyses for women and men, as well as different age groups, without finding convincing evidence of a strong association between overweight, obesity and risk for meningioma. These findings raise doubt that overweight and obesity *per se* are strongly associated with meningioma risk. Obviously, an underestimation of the effect of overweight and obesity on meningioma risk due to the long follow-up period in our study may be a contributing factor. However, in the much rarer tumor subgroups of PA and NST an association with overweight and obesity, consistent in subgroup analyses for sex and different age groups, could be demonstrated. Also, these associations remained stable in sensitivity analyses, excluding participants with 5 or less years of follow-up. In meningioma, the initially observed association with BMI per 5 kg/m^2 increase did not remain significant in sensitivity analysis and should not be overemphasized due to potential bias. Interestingly, the Me-Can cohort study provided some evidence for a positive association of metabolic factors with meningioma risk, indicating that there may be a more complex association between metabolic syndrome and meningioma risk which may explain the differing impact of BMI in relation to meningioma risk between studies [9]. Unfortunately, metabolic data were not available in our study, but should be assessed in future studies.

Overweight and obesity were not associated with glioma risk in this study. This is in congruence with other reports [6,7,10,16,19]. However, in their latest report, the IARC has stated that there was inadequate evidence for glioma to allow conclusions in regards presence or absence of a cancer-preventive effect of reducing body fatness, as the available data were of insufficient quality, consistency or statistical power [2]. We think, our study is a strong confirmation of the absence of an association between overweight, obesity and glioma risk, assessed for women and men in different age groups. We have also recently demonstrated that the absence of this association is consistent for different glioma subgroups [20].

Associations between BMI and risk for PA and NST have so far hardly been assessed. In the present study, we found evidence for positive associations between overweight, obesity and risk for PA in men and women. Yet, overweight and obesity were negatively associated with intracranial NST. This negative association has been indicated by two previous studies, but both had significant limitations in size and power [6,16]. However, in both tumor subgroups bias may represent a reasonable explanation for the effects seen: firstly, initially unrecognized hormone producing PAs may influence body weight or adolescent height (e.g. acromegaly or Cushing's disease). Secondly, vertigo and tinnitus, the most common symptoms associated with intracranial NSTs, may lead to secondary weight loss before diagnosis of NST. In both cases, reverse causality might explain the effects seen. To address this problem, we excluded participants with 5 years or less in follow-up time, which was considered a reasonable time interval from the onset of symptoms to diagnosis of a PA or NST. However, this did not change the associations seen between PA or NST risk and anthropometric measures, suggesting that reverse causality is unlikely.

Height and tumor risk

In this study, body height was positively associated with risk for meningioma, glioma, PA and NST. Our results are in congruence with other studies that have shown positive associations of height with glioma risk [7,8,15,19], while reports on meningioma risk have been inconsistent [6,7,10,11].

The association of height with risk for PA or NST has so far been unclear. For the first time, we report large cohort data suggesting a positive association between PA, NST and height.

Assessment of height in relation to tumor risk across different age groups demonstrated consistency in association with all tumor subgroups. This makes a birth cohort effect on height unlikely, which otherwise could have explained the overall association seen, as body height and the incidence of intracranial tumors have increased over the last decades [21].

The mechanisms underlying the association between height and intracranial tumor subgroups are unclear. Growth hormone (GH) and insulin-like growth factors (IGF-I and IGF-II) are important determinants of body height attained during childhood and adolescence and have previously been linked to the risk of other cancers [22,23]. Insulin-like growth-factor-binding-protein-2 (IGFBP-2) seems to play an important role in glioma cell proliferation, migration and invasion [24]. Overexpression of IGF-I and IGF-II mRNA transcripts has been demonstrated in glioma and meningioma [25]. A positive association between serum IGF-I and IGFBP-3 concentrations and intracranial schwannoma has been reported in a case-control study [26]. It has further been proposed, that infections in childhood may inhibit IGF-I and growth hormone production by induction of inflammatory responses representing a possible link between body height and the risk for intracranial tumor [19].

Study strengths and limitations

Strengths of this study are its large size including women and men of a wide age spectrum (14–80 years). Furthermore, height and weight were measured by trained personnel at the baseline examination, rather than self-reported by study participants. Linkage to the Cancer Registry of Norway, previously shown to provide incidence data of high quality, including completeness and validity [27], enabled the identification of intracranial tumors based on histopathology during follow-up. Reverse causality could be assessed with sufficient statistical power by excluding participants with 5 or less years of follow-up.

The main limitation of this study is the lack of information about other potential confounders, such as smoking, hormonally mediated factors or allergic conditions, previously suggested to be related to risk for intracranial tumor subgroups [13,28,29]. Furthermore, socio-economic status, previously shown to be related to height and BMI, may present a confounding factor that could not be accounted for in this study. However, studies that previously have reported an association between socio-economic status and risk for CNS tumors have not included height or BMI in the analyses [30–33]. Other studies that included both anthropometric data and socio-economic factors have not stated an association for socio-economic status with CNS tumor risk [7,8,10,15,16,34–36]. Therefore, there is no strong evidence that suggests significant bias of socio-economic status on the effect of height in regards CNS tumor risk.

Changes in BMI during follow-up could not be assessed in our study. BMI generally increases with aging and an association of small effect size between overweight or obesity and intracranial tumor risk could have been missed [37]. Also, the proportion of obese participants in our study population was smaller compared to other populations, which may increase the risk of an underestimation of the effect [38].

Due to the long follow-up period in our study, covering about four decades, changes in tumor incidence, mostly due to increasing detection rates over time need to be considered carefully in relation to anthropometric measures. As body height has been generally increasing in the younger generations in developed countries, this may bias the overall analysis, falsely indicating a true association between tumor risk and height. Therefore, the overall analyses were adjusted for birth cohorts and we further present data for different age strata as Supplementary tables. Although the stratified analyses for different age groups may indicate some differences between age groups, this is mostly due to smaller case numbers in the youngest age group as those have not reached their largest tumor incidence rates yet, as well as due to the larger confidence intervals and more imprecise point estimates in the highest age group which mainly reflects the lower detection rate in the 1970s and 1980s.

Ethnicity is an established risk factor for intracranial tumors [21,29,39]. As 99% of the eligible study population was Caucasian at the time of recruitment, our study's external validity to other populations of differing ethnicity is limited.

We could not differentiate intracranial tumors associated with familial tumor syndromes, such as neurofibromatosis 1 and 2, Li-Fraumeni or Turcot syndrome, from sporadic ones in our study. However, inherited cancer syndromes contribute only to a very minor proportion of intracranial tumors and were therefore not considered a major form of bias in this study.

Conclusions

In this study, height was associated with risk for all intracranial tumor subgroups, independently of sex or age group. This association was most pronounced for glioma and pituitary adenoma. Overweight and obesity were risk factors for PA, but seemed protective for intracranial NST. The association between BMI and meningioma risk may be more complex than so far assumed and metabolic factors associated with overweight and obesity may contribute to this association. This may explain the discrepancies in reported findings and further research on metabolic syndrome and intracranial tumor risk is warranted. However, this study does not support the recent announcement of the IARC for an association between body fatness and meningioma risk. Also, overweight and obesity can be quite confidently excluded as risk factors for glioma.

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Disclosure

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