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Anthropometric measures, physical activity and risk of glioma and meningioma in a large prospective cohort study

Dominique S. Michaud[1,2], **Gerald Bové**[1], **Valentina Gallo**[1], **Brigitte Schlehofer**[3], **Anne Tjønneland**[4], **Anja Olsen**[4], **Kim Overvad**[5], **Christina C. Dahm**[5,6], **Brigit Teucher**[3], **Heiner Boeing**[7], **Annika Steffen**[7], **Antonia Trichopoulou**[8,9], **Christina Bamia**[8], **Andreas Kyrozis**[9,10], **Carlotta Sacerdote**[11], **Claudia Agnoli**[12], **Domenico Palli**[13], **Rosario Tumino**[14], **Amalia Mattiello**[15], **H. Bas Bueno-de-Mesquita**[16,17], **Petra H. M. Peeters**[18], **Anne M. May**[18], **Aurelio Barricarte**[19,20], **Maria-Dolores Chirlaque**[20,21], **Miren Dorronsoro**[23], **Maria José Sánchez**[20,22], **Laudina Rodríguez**[24], **Eric J Duell**[25], **Göran Hallmans**[26], **Beatrice S. Melin**[27], **Jonas Manjer**[28], **Signe Borgquist**[29], **Kay-Tee Khaw**[30], **Nick Wareham**[31], **Naomi E. Allen**[32], **Ruth C. Travis**[32], **Isabelle Romieu**[33], **Paolo Vineis**[1], and **Elio Riboli**[1]

[1] Department of Epidemiology and Public Health, Imperial College, London, United Kingdom [2] Department of Community Health, Brown University, Providence, RI, USA [3] Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany [4] Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark [5] Department of Epidemiology, School of Public Health, Aarhus University, Denmark [6] Department of Cardiology, Aarhus University Hospital, Denmark [7] Department of Epidemiology, German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany [8] WHO Collaborating Center for Foodand Nutrition Policies, Department of Hygiene, Epidemiology and Medical Statistics, University of Athens Medical School, Athens, Greece [9] Hellenic Health Foundation, Athens, Greece [10] 1st Department of Neurology, Eginition Hospital, University of Athens Medical School, Athens, Greece [11] Department of Biomedical Science and Human Oncology, CPO-Piemonte, Torino, Italy [12] Nutritional Epidemiology Unit, Department of Preventive & Predictive Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy [13] Molecular and Nutritional Epidemiology Unit, ISPO-Cancer Research and Prevention Institute, Florence Italy [14] Cancer Registry and Histopathology Unit, "Civile -M.P. Arezzo" Hospital, ASP7 Ragusa, Italy [15] Department of Clinical and Experimental Medicine, Federico II University, Naples, Italy [16] National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands [17] Department of Gastroenterology and Hepatology, University Medical Centre Utrecht (UMCU), Utrecht, The Netherlands [18] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, the Netherlands [19] Public Health Institute of Navarra, Pamplona, Spain [20] CIBER Epidemiología y Salud Pública (CIBERESP), Spain [21] Department of Epidemiology, Regional Health Authority, Murcia, Spain [22] Andalusian School of Public Health, Granada, Spain [23] Public Health Division of Gipuzkoa, Basque Regional Health Department and Ciberesp., San Sebastian, Spain [24] Public Health and Participation Directorate, Health and Health Care Services Council, Asturias, Spain [25] Unit of Nutrition, Environment and Cancer, Cancer Epidemiology Research Programme, Catalan Institute of Oncology, Barcelona, Spain [26] Department of Public Health and Clinical Medicine, Nutritional Research, Umeå University, Umeå, Sweden [27] Department of Radiation Sciences, Oncology, Umeå University, Umeå, Sweden (Beatrice Melin) [28] Department of Plastic Surgery, Skåne University Hospital Malmö, Lund University, Malmö, Sweden [29] Department of Oncology, Skåne University Hospital Malmö, Lund University, Malmö, Sweden [30] Cancer Epidemiology Unit, University of Oxford, Nuffield Department of Clinical Medicine, Oxford,

Correspondence to: Dr. Dominique Michaud, Brown University, Box G-S121-2, Providence, RI 02912, Dominique_Michaud@brown.edu.

United Kingdom [31] Dept Public Health and Primary Care University of Cambridge, Cambridge, UK [32] MRC Epidemiology Unit, Cambridge, UK [33] International Agency for Research on Cancer (IARC), Lyon, France

Abstract

Body fatness has been associated with increased risk of a number of hormone-dependent cancers. Recent studies suggest that body mass index may be related to meningiomas, which are more common in women than men, and for which estrogens are believed to play a role. Using data from a large European propective cohort, 203 incident cases of meningioma and 340 cases of glioma were included in the analysis for measures of body fat, height, and physical activity among 380,775 participants. All analyses were conducted using Cox proportional hazards model and controlling for age, sex, country and education. A 71% increase in risk of meningioma was observed among men and women in the top quartile of waist circumference (HR = 1.71, 95% CI = 1.08–2.73, p-trend=0.01). A positive association was also observed for body mass index and meningioma (HR = 1.48, 95% CI = 0.98–2.23, for BMI ≥30 compared with a BMI of 20–24.9, *p* trend=0.05). An association with height and meningioma was also suggestive (HR = 1.24, 95% 0.96–1.51, for each 10cm increase). In contrast, no associations were observed for height and different measures of body fat and risk of glioma. Physical activity was not related to either type of brain tumors. Results from this study support an increase in risk of meningioma with higher body fatness among both men and women. No association was observed between anthropometric measures and risk of glioma.

Keywords

Brain tumors; glioma; meningioma; BMI; waist circumference; physical activity; cohort studies

Introduction

The worldwide obesity epidemic has severe health consequences, many of which are well known, and others which are less clear but are slowly being unravelled. The positive association between obesity and cancer is well established, and the number of cancers known to be affected by this condition has increased in the past decade as more data have emerged. In 2007, the World Cancer Research Fund (WCRF) report listed six cancers for which there is convincing evidence that body fatness increases risk (esophagus, postmenopausal breast, colorectal, endometrial, kidney, pancreas), and two for which the data are probable (gallbladder and liver)(1).

Brain tumors are rare and heterogenous, and consequently, epidemiological studies on these tumors have been faced with many challenges. To date, despite numerous case-control studies on brain tumors, only ionizing radiation and rare inherited genetic conditions have been established as risk factors for brain tumors (2). Allergies may decrease risk of glioma (3). The role of hormones is suspected for different subtypes of brain tumors, supported by large sex discrepancies in incidence rates by subtypes (4). Obesity influences endogenous hormone levels in the body by causing a number of metabolic changes, including increased androgen precursors for conversion to estrogen in peripheral tissue (5), and may possibility play a role in brain tumor development.

Two prospective cohort studies reported positive associations between body mass index (BMI) and risk of meningioma (6, 7) although a third cohort study found no association with meningioma (8). With respect to glioma, a large increase in risk was observed among

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individuals who were obese at age 18 years (NIH-AARP Diet and Health cohort)(9). Four other large cancer cohort studies examining obesity included ‘brain cancer’ as a site have been inconsistent (10–13). Four cohort studies reported positive associations with adult height (6, 8, 9, 14).

In a recent study, early life physical activity was associated with a lower risk of glioma, but not adult physical activity (9). Similarly, another cohort study reported no association with adult physical activity and glioma; however, a statistically significant inverse association was observed with meningioma (6). No other studies to date have examined physical activity and brain tumors.

Given the plausible role for obesity in brain tumor development and the paucity of data on this topic, we examine the association between anthropometric measurements (weight, height, waist circumference, waist to hip ratio (WHR)), physical activity and the relation to meningioma and glioma in a large European cohort study.

Methods

The European Prospective Investigation into Cancer and Nutrition (EPIC) is a multicenter prospective cohort study of participants from 23 centres located in Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom. The cohort was originally established to investigate the role of nutrition, physical activity, body size and other lifestyle factors, on the risk of developing cancer. Standardized questionnaires, anthropometric data, and country-specific food questionnaires were collected between 1992 and 2000 from a total of 519,978 participants (336,521 women and 153,457 men). Participants were mainly between 35 and 70 years of age at enrolment, and were recruited from the general population residing within defined geographic regions (i.e. towns or provinces), with some exceptions: women who were members of a health insurance scheme for state school employees (France), women attending breast cancer screening (Utrecht, The Netherlands, and Naples-Italy), blood donors (some centres in Italy and Spain), and predominantly vegetarians (Oxford ‘health conscious’ cohort). In most centres, subjects were then invited to provide a blood sample and to have anthropometric measurements taken. We refer the reader to Riboli et al. (15) for more details regarding study methodology.

Loss to follow-up (defined as unknown vital status at the last follow-up time) was lower than 6% across centres. Approval for the study was obtained from the ethical review boards of the participating institutions and from the International Agency for Research on Cancer.

Case ascertainment

Incident cancer cases (including benign brain tumors) were identified through linkage to population cancer registries in Denmark, Italy, The Netherlands, Norway, Spain, Sweden, and the UK, or with a combination of methods including linkage to health insurance records, cancer and pathology registries, and active follow-up of study participants or their next of kin in France, Germany, and Greece. France was not included in the current study as there were insufficient data to distinguish histology of the brain tumor at the time of the analysis. For all other countries, participants were followed from study entry (1991–2000) until first brain tumor diagnosis, death, emigration, or end of the follow-up period. The current analysis was based on the central dataset held at the International Agency for Research on Cancer data set, updated to April 2004. For centres using cancer registry data, censoring dates for complete follow-up were December 1999 (Turin, Italy), December 2000 (Asturias and Murcia, Spain; Cambridge, United Kingdom; Bilthoven, the Netherlands), December 2001 (Florence, Varese, Ragusa, and Naples, Italy; Granada, Norway, Navarra, and San

Sebastian, Spain; Oxford, United Kingdom; Malmö, Sweden), December 2002 (Umeå, Sweden; Aarhus and Copenhagen, Denmark), and June 2003 (Utrecht, the Netherlands).

We included all primary incident cases diagnosed with glioma (coded using International Classification of Diseases-Oncology [ICD-O] 2nd edition: 9380–9460, 9505) or meningioma (ICD-O-2 codes 9530–9537) through the end of follow-up. Over 98% of gliomas in this dataset were malignant; 5% of all meningiomas were malignant. Two of the five centres in Spain did not record data on benign tumors and reported no meningioma cases.

Anthropometry

All, but one, centres included in the current study had measured anthropometric factors at baseline; self-reported measures from the Oxford health-conscious volunteers included here were corrected for possible reporting bias (as overweight individuals tend to underestimate their weight). The corrections were obtained from age- and sex-specific regression of measured anthropometry onto self-reported anthropometry from the Oxford subjects recruited through general practitioners, for whom both measured and self-reported baseline anthropometry were available (16).

Height and weight were recorded to the nearest 0.1 kg and 0.1 or 0.5 cm, respectively. Waist circumference was measured either at the narrowest torso circumference (Italy; Cambridge, United Kingdom; and Utrecht, the Netherlands) or at the midpoint between the lower ribs and iliac crest (Bilthoven, the Netherlands; Potsdam, Germany; Malmö, Sweden; and Oxford, United Kingdom). In Spain, Greece, Denmark, and Heidelberg, Germany, a combination of methods was used, but the majority of participants were measured at the narrowest circumference. Hip circumference was measured at the widest circumference (Italy; Spain; Bilthoven, the Netherlands; Greece; and Malmö, Sweden) or over the buttocks (United Kingdom; Utrecht, the Netherlands; Germany; and Denmark). In most Italian centres, Spain, Germany, and Denmark, weight was measured in light underwear. In the centres of Turin; Umeå, Sweden; and Utrecht, the Netherlands, subjects wore normal clothing without shoes. In the remaining centres (Oxford-GP and Cambridge, United Kingdom; Bilthoven, the Netherlands; Greece; Malmö, Sweden), weighing was undertaken after removal of heavier sweaters or indoor jackets and emptying heavy objects from pockets (light clothing). Each participant’s body weight and waist and hip circumference was corrected to reduce heterogeneity due to protocol differences in clothing worn during measurement. For subjects who were normally dressed and without shoes, 1.5 kg for weight and 2.0 cm for circumferences were subtracted from the original measurement, while for subjects in light clothing without shoes 1 kg was subtracted from weight. The centres in Umeå, Sweden had measured height and weight at baseline but no values for hip and waist circumference; these centres were not included in the analyses on hip and waist circumference.

Physical Activity

In each centre, work, leisure-time/home, and vigorous physical activity were assessed at baseline as part of the standardized lifestyle questionnaire. The core physical activity questionnaire used by most centres included questions on type of physical activity at work and the number of hours spent each week on vigorous physical activity and a number of specific recreational and household activities, including walking, housework, sport, gardening, and do it yourself. A summary ‘leisure time’ physical activity variable was created by summing the number of hours spent per week in summer or winter on recreational and household or do-it-yourself physical activities. The intensities of these recorded activities were estimated from published values, and from these, summary leisure time metabolic equivalent (MET) levels were calculated as the sum of the MET hours/wk.

We used an index of the sum of recreational and occupational reported physical activity for this analysis; in a validation study within EPIC, the correlation between the index for the sum of recreational and occupational physical activity and objective measures of energy expenditure was higher (r=0.28, p<0.001) than when household activities were included (17).

Statistical Analysis—We excluded prevalent cancers at recruitment (except for non-melanoma skin cancer) and individuals with no follow-up data (n=27,082). After excluding France (missing histological data on cancer cases) and Norway (uncorrected self-reported weight only), and missing data on height or weight, 380,775 men and women were available for the main analysis.

Cox proportional hazard models were used in the analyses to estimate relative risk and 95% confidence intervals. Age at recruitment served as the underlying time matrix, with entry and exit time defined as the subject's age at recruitment and age at cancer diagnosis or censoring, respectively. Meningioma and glioma cancer incidence was considered for each body measure (BMI, height (cm), waist to hip ratio, waist circumference (cm), and weight (kg)) and physical activity. BMI was calculated as weight divided by height squared (kg/m^2) and subjects were categorized into 4 categories: BMI of <20.0, 20 to 24.9, 25 to 29.9, and ≥30 kg/m^2. Subjects were categorized according to sex-specific quartiles of height, weight, waist and hip circumference, and waist-to-hip ratio defined over the entire sex specific cohort, and using the lowest quartile as the referent category. All models were stratified by age, sex, centre and multivariate models were adjusted for education (none/primary, technical/professional, secondary, university) as higher education has been associated with brain tumors in some studies (and is also associated with obesity). Analyses of weight, waist and hip circumference, and waist-to-hip ratio were also adjusted for height and the analysis for physical activity was further adjusted for BMI. Adjusting for BMI, when examining central obesity measures (i.e., waist and hip circumference), did not change the estimates. Trend tests were calculated using the continuous anthropometric variables and across the categories of physical activity. All analyses were performed in SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Over 8.4 years of follow-up, a total of 203 cases of meningioma (55 men; 148 women) and 340 cases of glioma (167 men; 173 women) were newly diagnosed. Men and women with higher BMI were older (Table 1). Participants with higher BMIs were less likely to be current smokers than those with lower BMIs. The overall calculated METs for men decreased across categories of BMI but increased among women. Stature decreased across BMI categories for both men and women. Women with higher BMI were more likely to be postmenopausal women. Overall 16% of men and women were obese; only 0.4% of men were morbidly obese (BMI≥40), and 1% of women were morbidly obese women. BMI and fat distribution also varied by country, as previously reported (18).

Positive associations were observed between BMI, waist circumference, and weight and risk of meningioma (Table 2). The association for waist circumference was slightly attenuated when including BMI in the same model (comparing the top vs. bottom categories, HR = 1.43, 95% CI = 0.75–2.75). A 24% increase in risk was observed for each 10 cm increment in height, although this did not reach statistical significance (Table 2). Waist-to-hip ratio and physical activity were not associated with risk of meningioma. The associations for BMI and waist circumference and risk of meningioma were similar for men and women (Table 3). In contrast, we observed no association for BMI, height, weight, waist circumference, waist-to-hip ratio or physical activity and risk of glioma in this population (Table 2). Similarly, no associations were noted for these measures and risk of glioblastoma (n=184, ICD-0-2 9440/3; data not shown).

We had data on BMI at age 20 for a subset of this population (127,494 women and 73,834 men); no associations with those who were overweight (BMI>25) at 20 years of age and subsequent risk of either glioma (HR =1.06, 95% CI = 0.68–1.64); 23 cases BMI≥25; 177 cases BMI<25) or meningioma (HR = 0.91, 95% CI 0.45–1.82; 10 cases BMI≥25; 86 cases BMI<25). In this subset of the population, BMI at age 20 was correlated (r=0.48 p < 0.0001) with BMI at recruitment (on average 30 years later).

Discussion

In this large European cohort study, BMI, waist circumference and weight were associated with increased risk of meningioma. A suggestive association was observed for height and risk of meningioma, although the association was not statistically significant. No associations were observed for measures of obesity and risk of glioma.

Our results on measure of body fatness and risk of meningioma are consistent with the magnitude of associations in two other cohorts (6, 7). A 40% increase in the risk of meningioma was observed for obese women in the Million Women Study (390 meningioma; RR=1.40, 95% CI = 1.08–1.87, comparing BMI≥30 vs BMI <25)(6). In the Nurses' Health Study, a 61% increase in risk was observed for women with a BMI≥25 (125 meningioma; RR=1.61, 95% CI = 0.96–2.70, *p* for trend=0.06) (7). No association with BMI and meningioma was noted in a third prospective study (8).

The epidemiologic findings may support a role for endogenous hormones in the etiology of meningioma, although other mechanisms, including immune function and inflammation, may explain these findings, especially given that we also noted an association among men. In a recent publication, we reported elevated risk of meningioma among women taking hormone replacement therapy (HRT) in this cohort (19). The role of sex hormones in meningioma risk is supported by the well-known sex differences in rates of meningioma (2 fold higher in women than men(4)), case reports (20), and by biological data showing proliferation of meningioma cells with exposure to estradiol or progesterone (21).

Our null findings for the relationship between BMI and glioma was consistent with findings from large cohort studies; no association with adult BMI and glioma was reported in the NIH-AARP cohort (9) or the Million Women Study)(6). Two studies examining weight and total cancer mortality with data on brain and nervous system cancer did not report associations for obesity and brain (12, 13). However, a suggestive increase in risk of brain cancer with elevated weight was noted among male Koreans (11) and among women (only) in an Icelandic population (10).

We failed to detect an association between height and risk of glioma; however, a small increase in risk of meningioma cannot be ruled out. Positive associations with adult height and brain tumors have been previously observed in two large cohort studies. A 24% increase in risk of glioma was observed for each additional 10cm in stature in the Million Women Study (646 glioma; RR=1.24, 95% CI=1.09–1.40)(6). Height was also associated with a small increase in risk of meningioma in this cohort, but the association was not statistically significant (390 meningioma; RR = 1.11, 95% CI = 0.94–1.31) (6). In the NIH-AARP cohort, adult height of 1.90 cms or greater (compared to less than 1.60cms) was associated with a 2-fold increase in risk of glioma (480 glioma; RR=2.12, 9% CI = 1.18–3.81) and a dose-response relationship was observed (p=0.006)(9). Other cohorts using mortality endpoints or national cancer registries have reported positive associations with height and risk of malignant brain tumors (8, 14). It has been hypothesized that the link between adolescent height and cancer risk is predicated on insulin-like growth factor (IGF) levels during childhood (22). A very small nested case-control study (22 cases) reported a positive association between serum IGF-1 levels and glioma risk (23).

It has been proposed that early life exposures may influence glioma risk (24) and suggests that perhaps factors related to nutrition and energy balance in early life could alter adult risk of brain tumors. Our findings are in contrast to a recent cohort study that reported almost 4-fold increase in risk for glioma for participants who reported being obese at age 18 years (236 glioma; RR= 3.91, 95% CI = 2.08–7.35, BMI≥ 30 vs 18.5–24.9)(9). We had about half of the population numbers per category in comparison to the previous study; however, there were at least 30 cases of glioma in each category of BMI at age 20 and thus statistical power was not likely the explanation for the difference observed. We had no data on other early life measurements.

Only two studies to date have examined the relation between physical activity and brain cancer (6, 9). Our null finding for glioma is consistent with both of these studies, which reported no association for adult or adolescent physical activity. However, an inverse association was observed between strenuous physical activity and meningioma in the Million Women Study (6). The association for meningioma was inverse in our study, but the association was not statistically significant; the difference between the two studies may be due to measurement error in physical activity.

The major strength of this study is that anthropometric data were obtained by direct measurement of the participants at each centre during recruitment. Previous cohort studies have used self-reported anthropometric measurements (including the NIH-AARP Diet and Health cohort and the Million Women Study cohort). Those centres with only self-reported and unadjusted measurements for height and weight were excluded from this analysis to reduce measurement error (i.e., France and Norway). In addition, this study has the advantage of having close to complete follow-up over a mean of 8.4 years and the ability to identify and separate brain tumors by histology. One limitation to this study was that we had too few cases to examine associations by subgroups, e.g., premenopausal women.

Our findings support a positive association between body fatness and risk of meningioma, but not glioma. A small positive increase in risk of meningioma with height was observed, which is consistent with previous studies, although this association was not statistically significant. No associations were noted for physical activity and brain tumors. Future cohort studies are needed to examine these associations in greater depth.

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Cancer Research UK A11692 PI Dame Beral. valerie.beral@ndm.ox.ac.uk

Cancer Research UK Grant number C864/A8257 PI Kay-Tee Khaw kk101@medschl.cam.ac.uk

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Table 1

Characteristics across categories of body mass index in the EPIC cohort study, by sex.

Characteristic	Body Mass Index							
	Men				Women			
	<20	20–24.9	25–29.9	≥30	<20	20–24.9	25–29.9	≥30
Number of participants	2,818	49,235	70,303	22,463	15,549	106,498	75,997	37,645
Mean age at recruitment (SD)	47.3 (14)	50.6 (11)	53.0 (9.4)	53.7 (8.9)	44.2 (13)	48.8 (11)	52.9 (9.9)	54.0 (9.5)
Postmenopausal women (%)					28.9	39.1	51.6	54.4
Mean height in cm (SD)	176 (7.7)	176 (7.2)	174 (7.2)	173 (7.5)	164 (6.5)	163 (6.5)	161 (6.7)	159 (7.0)
Mean weight in kg (SD)	59.2 (5.9)	71.8 (6.8)	82.8 (7.7)	97.6 (11)	51.1 (4.7)	60.4 (5.7)	70.5 (6.6)	85.4 (11)
Mean Waist to Hip ratio (SD)	0.86 (0.05)	0.90 (0.05)	0.95 (0.05)	0.99 (0.06)	0.75 (0.05)	0.77 (0.06)	0.81 (0.07)	0.84 (0.07)
Mean waist circumference in cm (SD)	77.4 (5.5)	86.6 (5.9)	96.1 (6.2)	109 (8.3)	67.4 (4.6)	74.0 (6.0)	83.7 (7.1)	97.1 (10)
Smoking (%)								
Never	41.1	39.0	32.7	28.9	53.3	52.8	58.0	65.9
Former	18.8	30.3	39.0	42.1	19.4	24.0	22.5	19.2
Smoker	40.1	30.7	28.3	29.0	27.2	23.2	19.6	15.0
Mean total MET-h/week (SD)	69.5(42)	68.5 (42)	64.1 (42)	59.7 (42)	91.9 (50)	98.1 (51)	104.5 (52)	107.2 (52)
Mean physical activity index (SD)**	2.4 (1.1)	2.6 (1.1)	2.6 (1.1)	2.4 (1.1)	2.4 (1.0)	2.4 (1.0)	2.3 (1.1)	2.0 (1.0)

* All means (other than age) are age-adjusted using GLM procedure.

** Physical activity index does not include household activities (see Methods).

Table 2

Hazard ratios and 95% confidence intervals for anthropometric measures, physical activity and risk of glioma and meningioma in the EPIC cohort study

		Glioma		Meningioma	
	Person-years	**Cases**	**HR* (95% CI)**	**Cases**	**HR (95% CI)**
BMI (kg/m^2)					
<20	159,641	13	1.08 (0.60–1.92)	7	1.00 (0.46–2.19)
20–24.9	1,367,994	125	1.0 (referent)	70	1.0 (referent)
25–30	1,282,630	147	1.04 (0.81–1.34)	87	1.34 (0.97–1.86)
≥30	518,684	55	1.06 (0.76–1.48)	39	1.48 (0.98–2.23)
P-for trend			0.80		0.05
Per 5 kg/m^2			1.02 (0.89–1.17)		1.12 (0.95–1.32)
Height					
Quartile 1	830,086	82	1.0 (referent)	47	1.0 (referent)
Quartile 2	823,133	82	0.94 (0.68–1.29)	54	1.17 (0.78–1.78)
Quartile 3	851,286	87	0.98 (0.71–1.36)	43	0.88 (0.57–1.38)
Quartile 4	833,811	89	1.07 (0.77–1.50)	59	1.32 (0.86–2.05)
P-for trend			0.59		0.36
Per 10 cm			1.04 (0.87–1.24)		1.24 (0.96–1.51)
Weight					
Quartile 1	835,045	68	1.0 (referent)	36	1.0 (referent)
Quartile 2	838,752	99	1.33 (0.97–1.83)	47	1.18 (0.75–1.84)
Quartile 3	833,905	87	1.11 (0.79–1.54)	54	1.29 (0.83–2.01)
Quartile 4	824,785	86	1.11 (0.78–1.56)	66	1.51 (0.97–2.36)
P-for trend			0.86		0.02
Per 5 kg			1.01 (0.96–1.06)		1.06 (1.00–1.12)
Waist circumference					
Quartile 1	770,346	73	1.0 (referent)	32	1.0 (referent)
Quartile 2	787,522	82	0.90 (0.65–1.24)	45	1.18 (0.73–1.88)
Quartile 3	799,097	73	0.82 (0.59–1.16)	41	1.06 (0.65–1.72)
Quartile 4	774,325	90	0.97 (0.69–1.35)	66	1.71 (1.08–2.73)
P-for trend			0.81		0.01

		Glioma		Meningioma	
	Person-years	Cases	HR* (95% CI)	Cases	HR (95% CI)
Per 10 cm			1.03 (0.92–1.15)		1.14 (1.00–1.31)
Waist-to-Hip ratio (WHR)					
Quartile 1	782,141	75	1.0 (referent)	35	1.0 (referent)
Quartile 2	760,833	73	0.85 (0.62–1.19)	42	1.04 (0.66–1.65)
Quartile 3	810,804	78	0.82 (0.59–1.13)	46	0.99 (0.62–1.56)
Quartile 4	777,513	91	0.92 (0.66–1.28)	60	1.27 (0.81–1.99)
P-for trend			0.61		0.30
Per 0.1			0.98 (0.82–1.18)		1.06 (0.85–1.34)
Physical activity					
Quartile 1	734,276	69	1.0 (referent)	44	1.0 (referent)
Quartile 2	1,018,570	108	1.03 (0.75–1.42)	69	1.09 (0.73–1.62)
Quartile 3	680,230	74	1.06 (0.75–1.50)	34	0.83 (0.52–1.34)
Quartile 4	617,553	65	0.95 (0.66–1.37)	33	0.82 (0.50–1.36)

* Hazard Ratio (HR) and confidence intervals (CI) are from models stratified by age, country, sex and adjusted for education. In addition, models for weight, waist circumference and WHR models were adjusted for height; and physical activity model was adjusted for BMI.

** Waist circumference was not collected in some centres (missing 34,527).

Table 3

Hazard ratios and 95% confidence intervals for BMI, height, and waist circumference and risk of meningioma in the EPIC cohort study, by sex

	Men		Women	
	Cases	HR* (95% CI)	Cases	HR* (95% CI)
BMI (kg/m^2)				
<20	1	1.14 (0.15–8.64)	6	0.99 (0.43–2.33)
20–24.9	17	1.0 (referent)	53	1.0 (referent)
25–30	27	1.14 (0.62–2.12)	60	1.43 (0.98–2.10)
≥30	10	1.51 (0.68–3.37)	29	1.47 (0.91–2.36)
P-for trend		0.34		0.09
Per 5 kg/m^2		1.15 (0.79–1.66)		1.14 (0.95–1.36)
Height				
Quartile 1	8	1.0 (referent)	39	1.0 (referent)
Quartile 2	22	2.27 (0.99–5.29)	32	0.89 (0.55–1.45)
Quartile 3	9	0.91 (0.34–2.45)	34	0.89 (0.54–1.47)
Quartile 4	16	1.67 (0.67–4.22)	43	1.26 (0.77–2.08)
P-for trend		0.80		0.35
Per 10 cm		1.12 (0.74–1.70)		1.30 (0.98–1.71)
Waist circumference**				
Quartile 1	8	1.0 (referent)	24	1.0 (referent)
Quartile 2	15	1.72 (0.72–4.11)	30	0.98 (0.56–1.71)
Quartile 3	11	1.48 (0.58–3.76)	30	0.90 (0.50–1.59)
Quartile 4	14	1.81 (0.73–4.49)	52	1.59 (0.92–2.75)
P-for trend		0.26		0.02
Per 10 cm		1.15 (0.86–1.53)		1.14 (0.98–1.33)

* Hazard Ratio (HR) and confidence intervals (CI) are from models stratified by age, country, sex and adjusted for education. Additionally the waist circumference model was adjusted for height.

** Waist circumference was not collected in some centres (missing 34,527).