Anthropometric Measures, Physical Activity, and Risk of Glioma and Meningioma in a Large Prospective Cohort Study

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Abstract

Body fatness has been associated with increased risk of a number of hormone-dependent cancers. Recent studies suggest that body mass index (BMI) 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 prospective 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 = 0.01). A positive association was also observed for BMI and meningioma (HR = 1.48, 95% CI = 0.98–2.23, for BMI ≥30 compared with a BMI of 20–24.9, P = 0.05). An association with height and meningioma was also suggestive (HR = 1.24, 95% 0.96–1.51, for each 10 cm 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.

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 unraveled. 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 report listed 6 cancers for which there is...
Materials and Methods

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, and waist to hip ratio (WHR)], physical activity, and risk of meningioma and glioma in a large European cohort study.

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 United Kingdom, 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 data set held at the International Agency for Research on Cancer data set, updated to April 2004. For centers 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] second edition: 9380-9460, 9505) or meningioma (ICD-O-2 codes 9530-9537) through the end of follow-up. Over 98% of gliomas in this data set were malignant; 5% of all meningiomas were malignant. Two of the 5 centers in Spain did not record data on benign tumors and reported no meningioma cases.

Anthropometry

All, but one, centers included in this 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 regres-
sion 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
cam 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 combina-
tion of methods was used, but the majority of participants
were measured at the narrowest circumference. Hip cir-
cumference 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 centers, Spain, Germany, and Denmark,
weight was measured in light underwear. In the centers of
Turin; Umeå, Sweden; and Utrecht, the Netherlands,
subjects wore normal clothing without shoes. In the
remaining centers (Oxford-GP and Cambridge, United
Kingdom; Bilthoven, the Netherlands; Greece; Malmö,
Sweden), weighing was undertaken after removal of heav-
ier 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 because of 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, whereas for subjects in light clothing with-
out shoes 1 kg was subtracted from weight. The centers in
Umeå, Sweden had measured height and weight at baseline
but no values for hip and waist circumference; these centers
were not included in the analyses on hip and waist cir-
cumference.

Physical activity

In each center, 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 centers included ques-
tions 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 vari-
able was created by summing the number of hours spent
per week in summer or winter on recreational and house-
hold 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/week. We used an index of the sum of recrea-
tional 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 occupa-
tional 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
nonmelanoma skin cancer) and individuals with no fol-
low-up data ($n = 27,082$). After excluding France (miss-
ing histologic 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 ana-
lyses to estimate relative risk and 95% CIs. Age at recruit-
ment 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), WHR, 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 the following 4 cate-
gories: BMI less than 20.0, 20 to 24.9, 25 to 29.9, and 30 kg/
m$^2$ or more. Subjects were categorized according to sex-
specific quartiles of height, weight, waist and hip circum-
ference, and WHR defined over the entire sex-specific
cohort, and using the lowest quartile as the referent cate-
gory. All models were stratified by age, sex, center, 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 WHR were also
adjusted for height, and the analysis for physical activity was
further adjusted for BMI. Adjusting for BMI, when examin-
ing central obesity measures (i.e., waist and hip circum-
fERENCE), did not change the estimates. Trend tests were
calculated using the continuous anthropometric variables
and across the categories of physical activity. All analyses
were carried out in SAS version 9.2 (SAS Institute Inc.).

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. Over-
all 16% of men and women were obese; only 0.4% of men
(BMI $\geq 40$) and 1% of women were morbidly obese. 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). WHR 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, WHR, 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 were observed for 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) compared to those who had a normal weight (BMI <25) at age 20 (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 2 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; ref. 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_trend = 0.06; ref. 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 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; ref. 4), case reports (20), and by biological data showing proliferation of meningioma cells with exposure to estradiol or progesterone (21).

Table 2. HRs and 95% CIs for anthropometric measures, physical activity, and risk of glioma and meningioma in the EPIC cohort study

<table>
<thead>
<tr>
<th>Measure</th>
<th>Person-years</th>
<th>Glioma Cases</th>
<th>HR* (95% CI)</th>
<th>Meningioma Cases</th>
<th>HR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>159,641</td>
<td>13</td>
<td>1.08 (0.60–1.92)</td>
<td>7</td>
<td>1.00 (0.46–2.19)</td>
</tr>
<tr>
<td>20–24.9</td>
<td>1,367,994</td>
<td>125</td>
<td>1.0 (referent)</td>
<td>70</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>25–30</td>
<td>1,282,630</td>
<td>147</td>
<td>1.04 (0.81–1.34)</td>
<td>87</td>
<td>1.34 (0.97–1.86)</td>
</tr>
<tr>
<td>≥30</td>
<td>518,684</td>
<td>55</td>
<td>1.06 (0.76–1.48)</td>
<td>39</td>
<td>1.48 (0.98–2.23)</td>
</tr>
<tr>
<td>Ptrend</td>
<td></td>
<td></td>
<td>0.80</td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>Per 5 kg/m²</td>
<td></td>
<td></td>
<td>1.02 (0.89–1.17)</td>
<td>1.12 (0.95–1.32)</td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile 1</td>
<td>830,086</td>
<td>82</td>
<td>1.0 (referent)</td>
<td>47</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>Quartile 2</td>
<td>823,133</td>
<td>82</td>
<td>0.94 (0.68–1.29)</td>
<td>54</td>
<td>1.17 (0.78–1.78)</td>
</tr>
<tr>
<td>Quartile 3</td>
<td>851,286</td>
<td>87</td>
<td>0.98 (0.71–1.36)</td>
<td>43</td>
<td>0.88 (0.57–1.38)</td>
</tr>
<tr>
<td>Quartile 4</td>
<td>833,811</td>
<td>89</td>
<td>1.07 (0.77–1.50)</td>
<td>59</td>
<td>1.32 (0.86–2.05)</td>
</tr>
<tr>
<td>Ptrend</td>
<td></td>
<td></td>
<td>0.59</td>
<td></td>
<td>0.36</td>
</tr>
<tr>
<td>Per 10 cm</td>
<td></td>
<td></td>
<td>1.04 (0.87–1.24)</td>
<td>1.24 (0.96–1.51)</td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile 1</td>
<td>835,045</td>
<td>68</td>
<td>1.0 (referent)</td>
<td>36</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>Quartile 2</td>
<td>838,752</td>
<td>99</td>
<td>1.33 (0.97–1.83)</td>
<td>47</td>
<td>1.18 (0.75–1.84)</td>
</tr>
<tr>
<td>Quartile 3</td>
<td>833,905</td>
<td>87</td>
<td>1.11 (0.79–1.54)</td>
<td>54</td>
<td>1.29 (0.83–2.01)</td>
</tr>
<tr>
<td>Quartile 4</td>
<td>824,785</td>
<td>86</td>
<td>1.11 (0.78–1.56)</td>
<td>66</td>
<td>1.51 (0.97–2.36)</td>
</tr>
<tr>
<td>Ptrend</td>
<td></td>
<td></td>
<td>0.86</td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>Per 5 kg</td>
<td></td>
<td></td>
<td>1.01 (0.96–1.06)</td>
<td>1.06 (1.00–1.12)</td>
<td></td>
</tr>
<tr>
<td>Waist circumferenceb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile 1</td>
<td>770,346</td>
<td>73</td>
<td>1.0 (referent)</td>
<td>32</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>Quartile 2</td>
<td>787,522</td>
<td>82</td>
<td>0.90 (0.65–1.24)</td>
<td>45</td>
<td>1.18 (0.73–1.88)</td>
</tr>
<tr>
<td>Quartile 3</td>
<td>799,097</td>
<td>73</td>
<td>0.82 (0.59–1.16)</td>
<td>41</td>
<td>1.06 (0.65–1.72)</td>
</tr>
<tr>
<td>Quartile 4</td>
<td>774,325</td>
<td>90</td>
<td>0.97 (0.69–1.35)</td>
<td>66</td>
<td>1.71 (1.08–2.73)</td>
</tr>
<tr>
<td>Ptrend</td>
<td></td>
<td></td>
<td>0.81</td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Per 10 cm</td>
<td></td>
<td></td>
<td>1.03 (0.92–1.15)</td>
<td>1.14 (1.00–1.31)</td>
<td></td>
</tr>
<tr>
<td>WHR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile 1</td>
<td>782,141</td>
<td>75</td>
<td>1.0 (referent)</td>
<td>35</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>Quartile 2</td>
<td>760,833</td>
<td>73</td>
<td>0.85 (0.62–1.19)</td>
<td>42</td>
<td>1.04 (0.66–1.65)</td>
</tr>
<tr>
<td>Quartile 3</td>
<td>810,804</td>
<td>78</td>
<td>0.82 (0.59–1.13)</td>
<td>46</td>
<td>0.99 (0.62–1.56)</td>
</tr>
<tr>
<td>Quartile 4</td>
<td>777,513</td>
<td>91</td>
<td>0.92 (0.66–1.28)</td>
<td>60</td>
<td>1.27 (0.81–1.99)</td>
</tr>
<tr>
<td>Ptrend</td>
<td></td>
<td></td>
<td>0.61</td>
<td></td>
<td>0.30</td>
</tr>
<tr>
<td>Per 0.1</td>
<td></td>
<td></td>
<td>0.98 (0.82–1.18)</td>
<td>1.06 (0.85–1.34)</td>
<td></td>
</tr>
<tr>
<td>Physical activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile 1</td>
<td>734,276</td>
<td>69</td>
<td>1.0 (referent)</td>
<td>44</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>Quartile 2</td>
<td>1,018,570</td>
<td>108</td>
<td>1.03 (0.75–1.42)</td>
<td>69</td>
<td>1.09 (0.73–1.62)</td>
</tr>
<tr>
<td>Quartile 3</td>
<td>680,230</td>
<td>74</td>
<td>1.06 (0.75–1.50)</td>
<td>34</td>
<td>0.83 (0.52–1.34)</td>
</tr>
<tr>
<td>Quartile 4</td>
<td>617,553</td>
<td>65</td>
<td>0.95 (0.66–1.37)</td>
<td>33</td>
<td>0.82 (0.50–1.36)</td>
</tr>
</tbody>
</table>

*HR and CIs 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; physical activity model was adjusted for BMI.

bWaist circumference was not collected in some centers (missing 34,527).
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; ref. 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 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 with elevated weight was noted among male Koreans (11) and among women (only) in an Icelandic population (10).

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 (236 glioma; RR = 3.91, 95% CI = 2.08–7.35, BMI ≥ 30 vs. 18.5–24.9; ref. 9). We had about half of the population numbers per category in comparison with 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 2 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,

<table>
<thead>
<tr>
<th>Table 3. HRs and 95% CIs for BMI, height, and waist circumference and risk of meningioma in the EPIC cohort study, by sex</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
</tr>
<tr>
<td><strong>Cases</strong></td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong>&lt;br&gt;＜20</td>
</tr>
<tr>
<td>20–24.9</td>
</tr>
<tr>
<td>25–30</td>
</tr>
<tr>
<td>≥30</td>
</tr>
<tr>
<td><strong>P_trend</strong></td>
</tr>
<tr>
<td>Per 5 kg/m²</td>
</tr>
<tr>
<td><strong>Height</strong>&lt;br&gt;Quartile 1</td>
</tr>
<tr>
<td>Quartile 2</td>
</tr>
<tr>
<td>Quartile 3</td>
</tr>
<tr>
<td>Quartile 4</td>
</tr>
<tr>
<td><strong>P_trend</strong></td>
</tr>
<tr>
<td>Per 10 cm</td>
</tr>
<tr>
<td><strong>Waist circumference</strong>&lt;br&gt;Quartile 1</td>
</tr>
<tr>
<td>Quartile 2</td>
</tr>
<tr>
<td>Quartile 3</td>
</tr>
<tr>
<td>Quartile 4</td>
</tr>
<tr>
<td><strong>P_trend</strong></td>
</tr>
<tr>
<td>Per 10 cm</td>
</tr>
</tbody>
</table>

*HR and CIs are from models stratified by age, country, sex, and adjusted for education. In addition, the waist circumference model was adjusted for height.

*Waist circumference was not collected in some centers (missing 34,527).
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 2 studies may be due to change or because of 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 center 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 centers 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, for example, 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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No potential conflicts of interest were disclosed.

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