HEIGHT, BODY MASS INDEX
AND
RISK FOR PRIMARY TUMOURS OF THE
CENTRAL NERVOUS SYSTEM

THESIS FOR THE DEGREE OF PHILOSOPHIAE DOCTOR

BY

MARKUS K.H. WIEDMANN

FACULTY OF MEDICINE, UNIVERSITY OF OSLO

AND

DEPARTMENT OF NEUROSURGERY, OSLO UNIVERSITY HOSPITAL

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ACKNOWLEDGEMENTS

The idea for this thesis was born in 2009 when I accidentally stumbled over the HUNT database and thought it would be worthwhile linking it to the Cancer Registry of Norway for identification of CNS tumours. Proposing this idea to Prof. Eirik Helseth, he was immediately enthusiastic about it and arranged a meeting with Prof. John Anker Zwart who, which I did not know at that time, had already been working extensively with the HUNT database in other regards. Thus, the foundation for this thesis was established!

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PAPERS INCLUDED IN THIS THESIS

Paper I:

Body Mass Index and the Risk of Meningioma, Glioma and Schwannoma in a Large Prospective Cohort Study (the HUNT Study)


Paper II:

Smoking, obesity and the risk of pituitary adenoma: a large prospective cohort study (The HUNT Study)


Paper III:

The impact of body mass index and height on risk for glioblastoma and other glioma subgroups: a large prospective cohort study


Paper IV:

Overweight, obesity and height as risk factors for glioma, meningioma, pituitary adenoma and nerve sheath tumour: Results from a large prospective cohort study

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>CNS</td>
<td>central nervous system</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<td>GBM</td>
<td>glioblastoma multiforme</td>
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<td>IDH</td>
<td>isocitrate dehydrogenase</td>
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<td>CBTRUS</td>
<td>Central Brain Tumour Registry of the US</td>
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<td>NOS</td>
<td>not otherwise specified</td>
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<td>NST</td>
<td>nerve sheath tumour</td>
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<td>PA</td>
<td>pituitary adenoma</td>
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<tr>
<td>IARC</td>
<td>International Agency for Research on Cancer</td>
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<tr>
<td>EPIC</td>
<td>European Prospective Investigation into Cancer and Nutrition</td>
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<tr>
<td>BMI</td>
<td>body mass index</td>
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<tr>
<td>HUNT</td>
<td>Helseundersøkelse Nord-Trøndelag</td>
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<tr>
<td>SSU</td>
<td>Statens Skjermbildeundersøkelse</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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<td>HR</td>
<td>hazard ratio</td>
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<td>IGF</td>
<td>insulin-like growth factor</td>
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<td>GH</td>
<td>growth hormone</td>
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<td>IGFBP</td>
<td>insulin-like growth factor binding protein</td>
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<td>Me-Can</td>
<td>Metabolic Syndrome and Cancer Project</td>
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INTRODUCTION

DEFINITION AND DESCRIPTIVE EPIDEMIOLOGY

Primary tumours of the central nervous system (CNS) comprise tumours of the brain and spinal cord, including tumours of leptomeningeal origin and tumours of the pituitary gland. Although primary CNS tumours only account for approximately 3.5% of all malignancies, of which a large proportion consists of benign histopathology, their specific anatomical location is associated with significant morbidity and mortality, and treatment is often challenging. While the term “CNS tumour” includes tumours of the whole neuraxis and its surrounding leptomeninges, the commonly used expression “brain tumour” comprises tumours located in and around the brain, although these tumours differ largely in histogenesis and behaviour.

Incidence rates for CNS tumours have increased significantly over the last decades, mostly as a result of better imaging techniques and their accessibility as well as improvements in systematic registration. Thus, in the United States, the annual incidence of CNS tumours per 100,000 persons was 11.5 in the period 1990-1994, whereas the recently reported age-adjusted overall incidence rates were 20-29 per 100,000 person-years.

Meningioma is the most common primary CNS tumour, representing approximately 36% of such tumours, followed by diffuse gliomas [World Health Organization (WHO) grade II–IV], accounting for 23% (Figure 1). Glioblastoma (GBM), the most aggressive and lethal of the malignant primary CNS tumours, represents 15% of all primary CNS tumours and is the most common malignant CNS tumour in adults. Tumours of the pituitary gland (16%) and nerve sheath tumours (NST) (8%) represent the 3rd and 4th largest primary CNS tumour subgroups. Vestibular schwannoma represents the vast majority (94%) of all nerve sheath tumours in the CNS.
Gliomas constitute a heterogeneous group of primary CNS tumours that arise from glial or precursor cells. The most common histological subgroups in adults include GBM, diffuse astrocytoma (WHO grade II and III), oligodendroglioma, oligoastrocytoma and malignant glioma not otherwise specified (NOS) (Figure 2). GBM is the most common malignant brain tumour in adults, and the prognosis is devastating, regardless of all treatment efforts, with a median overall survival of 10 to 15 months. The classification of glioma has recently been modified by the updated 4th edition 2016 WHO diagnostic criteria for primary CNS tumours (Figure 3). In contrast to the previous classification, in which diffuse astrocytoma, oligodendroglioma and oligoastrocytoma were distinct glioma subgroups based on morphologic criteria, the new classification instead uses molecular factors, i.e. isocitrate dehydrogenase (IDH) mutation and 1p/19q codeletion.
status for subgroup differentiation, with the aim of achieving more homogeneous diagnostic entities and improving diagnostic accuracy.\textsuperscript{10}

Figure 2  Distribution of glioma subgroups by morphology (data from the CBTRUS statistical report)\textsuperscript{10}
Figure 3  Updated WHO 2016 diagnostic algorithm for diffuse glioma diagnosis (adapted from Louis et al.)\textsuperscript{10}; NOS not otherwise specified
RISK FACTORS

Several potential risk factors for CNS tumours have been assessed previously, yet there are only a few established. Those are discussed below, together with some other variables that seemed relevant to our study or where increasing evidence suggests relevant associations with tumour risk.

AGE, GENDER AND ETHNICITY

The incidence of primary CNS tumours varies with age, gender and ethnicity. Meningioma incidence continuously increases with age, with a more than threefold higher risk in the 7th decade of life than in the 4th.1,3 Furthermore, meningioma is about two and a half times more common in women than men and significantly more common among Blacks than Caucasians.1,3,12,13

For glioma, the association with age differs by glioma subtype. While pilocytic astrocytoma is the most common glioma in children, diffuse low-grade glioma has its peak incidence in the 3rd and 4th decades of life, and GBM in the 6th and 7th decades.1 Furthermore, gliomas have a higher incidence rate in Caucasian than in Black or Hispanic ethnicities and are slightly more common in men than women.14

Pituitary adenoma (PA) incidence is slightly higher in women compared to men and higher in Black than in Caucasian, Hispanic or Asian ethnicities.15 Incidence peaks for PA were reported in the 3rd and 7th decades of life in women, while there was only one large incidence peak in the 7th decade in men.15

Intracranial NST, the large majority of cases being unilateral vestibular schwannomas, have a peak incidence in the 4th to 6th decades of life and no strong sex predilection.16,17 Although the evidence is weak, NST seem more common in Caucasian than in Black, Hispanic or Asian ethnicities.1,17

GENETICS

The large majority of primary CNS tumours occur sporadically, and only approximately 1-5% are linked to genetic syndromes.12,18,19 The most common hereditary syndromes that can cause primary CNS tumours include Neurofibromatosis I and II, tuberous sclerosis, von Hippel-Lindau disease, Li-Fraumeni syndrome and Turcot syndrome.12,18,19
Additionally, in approximately 3% of CNS tumours, a familial clustering of CNS tumour subtypes has been observed.\textsuperscript{20} Additional support for a polygenetic susceptibility has been obtained from genome-wide association studies, identifying different loci of single-nucleotide polymorphisms that are associated with CNS tumour risk.\textsuperscript{21,22}

**IONIZING RADIATION AND ELECTROMAGNETIC FIELDS**

Ionizing radiation is the only established environmental risk factor for primary CNS tumours, including glioma, meningioma and NST. This has been demonstrated in studies of atomic bomb survivors,\textsuperscript{23-27} in children irradiated for benign conditions such as tinea capitis or skin haemangioma\textsuperscript{18,32} and for radiation therapy of primary malignancies.\textsuperscript{33-39}

A recent meta-analysis has further estimated the excess relative risk, a measure of cancer risk per radiation dose, to assess the relation between ionizing radiation dose and risk for primary CNS tumours.\textsuperscript{40} This study indicated that ionizing radiation had a greater impact on meningioma incidence compared to glioma. There is also increasing evidence that low-dose ionizing radiation, as, for example, from diagnostic computed tomography scans of the head, may increase the risk of CNS tumours in children and young adults.\textsuperscript{41,42}

Since the 1990s, there has been a steep increase in mobile phone use, reaching 63% of the world population in 2016, and in Norway, nearly everyone uses a mobile phone (www.statista.com). The ubiquitous regular use of mobile phones in proximity to the head has raised concerns about harmful effects by radiofrequency electromagnetic fields. In 2011, the WHO International Agency for Research on Cancer (IARC) classified mobile phones as a possible human carcinogen. However, the evidence of an association between brain tumour risk and mobile phone use is weak and predominantly based on retrospective case-control studies.\textsuperscript{43,53} In the INTERPHONE study, one of the largest multinational case-control studies assessing the risk for CNS tumours in relation to mobile phone use, no association between mobile phone use and risk for meningioma or glioma was reported.\textsuperscript{54} Only two prospective cohort studies have assessed the risk for brain tumours in association with mobile phone use and did not support the hypothesis of an increased tumour risk for meningioma or glioma.\textsuperscript{55,56} However, one of them reported an increased risk for vestibular schwannoma among long-term users versus non-users of mobile phones (RR 2.46; 95% CI 1.07-5.64).\textsuperscript{56}

This association was not supported by the INTERPHONE study results or another recent large case-control study.\textsuperscript{57,58}
ALLERGY

There is some evidence, predominantly from case-control studies, indicating an inverse association between self-reported allergies and risk for glioma. This has recently been summarized in an updated meta-analysis, estimating the association between allergic condition and glioma risk (OR = 0.78, 95% CI 0.73–0.83, P < 0.001). This association has received some support from studies assessing serum IgE levels in relation to risk for different primary CNS tumours. Allergen-specific IgE levels measured in prediagnostic serum samples of brain tumour patients indicated an inverse association with glioma risk (although of borderline significance), but not for meningioma or schwannoma, in a case-control study nested in the EPIC (European Prospective Investigation into Cancer and Nutrition) cohort. Another case-control study based on biobank serum sample analyses of allergen-specific and total IgE levels linked to the Cancer Registry of Norway found a negative association between elevated allergen-specific IgE levels and GBM in women, but not in men. For glioma risk, there was no significant association with allergen-specific IgE levels in either women or men. Furthermore, there was no dose response seen in either GBM or glioma risk associated with allergen-specific IgE levels. Total IgE levels were negatively associated with glioma risk in women and men combined (OR 0.75 95% CI 0.56–0.99) but were not significantly associated with GBM risk (OR 0.74 95% CI 0.52–1.05).

A large multinational case-control study recently reported an inverse association between history of any allergy and glioma (OR = 0.73, 95% CI 0.60–0.88), meningioma (OR = 0.77, 95% CI 0.63–0.93), and acoustic neuroma (OR = 0.64, 95% CI 0.49–0.83), but information or selection bias and reverse causality were suspected as an explanation for the reported effects by the authors. Furthermore, no association was found between allergic condition and meningioma risk in an updated meta-analysis (OR 0.91, 95% CI 0.79–1.04), confirming the results of a previous meta-analysis. However, only 8 studies contributed original data to this meta-analysis, including only one prospective cohort study, which was underpowered.

TOBACCO SMOKING AND ALCOHOL CONSUMPTION

Tobacco smoking and alcohol consumption are known risk factors for several cancers, including cancers of the lung, oral cavity, larynx, pharynx, oesophagus, stomach, colon, and rectum. Tobacco smoke is a major environmental source of carcinogens including
polycyclic hydrocarbons and N-nitroso compounds, and components of smoke and alcohol can penetrate the blood-brain barrier.\textsuperscript{67,68}

So far, there is little evidence that tobacco smoking is associated with increased risk for glioma in women or men.\textsuperscript{69-76} Also, the association between alcohol consumption and risk for primary CNS tumours has been inconsistent, hampered by small numbers of cases, incongruence in definition of dependent variables and confounding.\textsuperscript{12,69,72,74,76-80}

The association of tobacco smoking with risk for meningioma has recently been reviewed in a meta-analysis, and no association was found.\textsuperscript{81} However, this meta-analysis consisted of only 8 studies with differing methodological quality and included only one large prospective cohort study.\textsuperscript{74} A more recent large case-control study examined smoking in relation to meningioma risk in women and men separately and found a decreased meningioma risk in females who had ever smoked (OR 0.8; 95\% CI, 0.7–0.9), while it was increased in men (OR 1.3; 95\% CI, 1.0–1.7).\textsuperscript{82} This study also included a meta-analysis of six other studies, of which only one was a prospective cohort study.\textsuperscript{82} In this analysis, women who reported “ever having smoked” were at decreased risk for meningioma (OR 0.82; 95\% CI, 0.68–0.98), while men who had ever smoked had an increased risk (OR 1.39; 95\% CI 1.08–1.79). However, the results for men were predominantly driven by one case-control study, and retrospective self-reporting of cigarette smoking must be considered a significant limitation. Additionally, the risk reduction in women was not dose dependent or different for current and past smokers. For men, there seemed to be a dose response for the duration of smoking and number of pack-years (both as binary variables) but no difference for current or past smokers.\textsuperscript{82} However, these results were based on small numbers of cases and controls, and the association between smoking and meningioma risk therefore remains unclear.

Studies specifically assessing smoking or alcohol consumption in association with PA or NST risk are scarce. For schwannoma, the only two studies we identified have indicated a protective effect of smoking for tumour risk.\textsuperscript{53,84}
There is a worldwide epidemic of growing body fatness (i.e. overweight and obesity), with a six fold increase in the proportion of obese [body mass index (BMI) ≥30 kg/m²] adults from 1975 to 2014 and a doubling of the rate of obese children and adolescents from 1980 to 2013. Recently, the age-standardized prevalence of obesity in adults has been estimated to be 11% in men and 15% in women. Over a decade ago, the IARC concluded that there is substantial evidence that the avoidance of overweight and obesity helps prevent cancers of the colon, breast (in postmenopausal women), endometrium and kidney (renal cell carcinoma), as well as adenocarcinoma of the oesophagus. Since then, additional cancers associated with body fatness have been identified and excess body weight has been confirmed as one of the most important preventable causes of cancer, particularly in high-income countries. A recent study has estimated that 8-10% of all cancers in women and 4% of all cancers in men in the United States and the United Kingdom are attributable to body fatness. Further, the proportion of all deaths from cancer that is attributable to overweight and obesity in U.S. adults 50 years of age or older may be as high as 14% in men and 20% in women.

Body height has been recognized as a factor associated with an increased incidence of many cancers, including cancers of the kidney, colorectum, lung, breast, prostate and ovary. A meta-analysis of height and risk for cancer has estimated a 10-15% increased overall cancer risk per 10 cm increase in height.

At the initiation of our study in 2010, the association between anthropometric factors and CNS tumour subgroups was largely unclear.

While height was associated with glioma risk in two cohort studies based on self-reported measures, this was more inconsistent in another study measuring height and weight at study inclusion prospectively. Overweight and obesity were not associated with glioma risk in previous studies, yet a study by Moore et al. indicated that overweight and obesity at the age of 18 increased the risk for glioma.

To our knowledge, only two studies have reported the association between meningioma risk and height at the time of initiation of our study. Of those, Benson et al. did not report a significant association in a large prospective cohort study of middle-aged women, while Helseth et al. found an association between height and CNS tumour risk overall, which was also reflected in the category of meningioma but did not reach
significance.\textsuperscript{74,99} Overweight and obesity in relation to meningioma risk have been reported on by four previous studies.\textsuperscript{74,99-101} While the study by Helseth et al. did not report a significant association, Benson et al. found an increased risk for meningioma in obese middle-aged women. Jhawar et al. also reported an association with meningioma risk in women with a BMI greater than 25 kg/m\textsuperscript{2}, although the results did not reach significance.\textsuperscript{100} A small case-control study by Bellur et al. reported an increased risk for meningioma in women and men, yet the definition of obesity was based on the subjective opinion of the patients’ examiner.\textsuperscript{101}

At the time of initiation of our study, there were hardly any data about the association between anthropometric measures and risk for PA, and only one study reported data for NST risk in relation to BMI and height, without finding any significant association.\textsuperscript{99}

**Methodological Considerations for Investigating Potential Risk Factors**

While the highest level of evidence for the efficacy of any medical treatment can only be achieved in a randomized controlled trial, this is not a feasible design to examine epidemiological risk factors. Obviously, study participants cannot be randomized to different groups of height, body fatness or socioeconomic status or to potentially harmful exposures such as smoking or alcohol consumption. Therefore, evidence in epidemiological research is derived from observational studies, in particular case-control and cohort studies. The main difference between those two is that in a case-control study, subjects with the outcome of interest (i.e. diagnosis of a CNS tumour) and unaffected controls are identified and the exposure of interest is retrospectively assessed, whereas in a cohort study, information on a defined cohort of subjects is gathered at baseline and the outcome of interest is recorded during prospective follow-up. The case-control study design is often chosen when the outcome of interest is rare. Subjects with that particular outcome can then be accumulated from a large population basis and compared to selected controls. The exposures of interest are then retrospectively assessed for each subject by questionnaires or examinations. Because one does not wait for the outcome of interest to occur (in contrast to cohort studies), this makes the case-control study quicker and easier to perform and may assure more statistical power in rare outcomes. However, there are several important challenges with case-control studies. One is the selection of appropriate controls. Ideally, controls should be as similar as possible to the cases apart from the outcome of interest. However, such a
control group may be differently exposed to the variable of interest. If, for example, the association between body fatness and risk for a certain cancer is investigated and control subjects are patients from the same hospital admitted for another reason (as commonly performed in case-control studies) the association to be investigated may be underestimated. As body fatness is also a risk factor for other conditions that may lead to hospital admission in the control group, this may bias the results of the study. Another main limitation of case-control studies is recall bias. As information in case-control studies is retrospectively obtained by questionnaires or interviews of the study subjects, the condition of interest (i.e. diagnosis of a CNS tumour) may influence the awareness of certain behaviours. This is more likely the case for conditions or behaviour that are commonly thought to be harmful, as for example obesity, diet, cigarette smoking or alcohol consumption. This may lead to an overestimation of the exposure to be examined due to underreporting in the control group or vice versa.

In a cohort study, a group of subjects is defined by certain selection criteria (the cohort) and information obtained at baseline. The cohort is then prospectively followed over time, and the outcome of interest (i.e. CNS tumour diagnosis) is recorded. If the outcome of interest is rare (as it is for different CNS tumour subgroups), a long follow-up and a large cohort are needed. Therefore, cohort studies are time consuming, costly and, in the case of rare outcomes, prone to be underpowered. Additionally, conclusions derived from a cohort study apply only to comparable cohorts and cannot necessarily be extrapolated to other subjects (external validity). Therefore, selection of subjects and definition of the study cohort at baseline need to be considered carefully when designing a cohort study. Another challenge with cohort studies is loss to follow-up. This means that not all subjects can be followed for the full length of the study due to different reasons (e.g. emigration). This is of particular concern if loss to follow-up occurs especially in predefined risk categories (i.e. cigarette smokers). Long-term follow-up also contains potential difficulties, as a subject’s exposure to risk factors may change over time, and information about those changes is rarely collected. Obviously, repeated assessments over time increase both the complexity and the cost of cohort studies. However, cohort studies can be considered the preferred method for observational studies due to their prospective design.
OBJECTIVES

The main objective of this thesis was to study the association of anthropometric data with risk for different CNS tumour subgroups. For this purpose, two independent large prospective population-based cohorts of Norwegian residents, i.e. the Helseundersøkelse Nord-Trøndelag (HUNT) and the Statens Skjermbildeundersøkelse (SSU), were linked to the Cancer Registry of Norway. In both cohorts, height and weight were measured at study baseline. While the HUNT study includes a variety of different variables attained through questionnaires, the SSU study is much larger in size but lacks information on other potentially confounding variables. Thus, the two databases have different methodological challenges, and a combined approach was thought to increase the impact in contributing to a better understanding of the hypothesized associations.

Paper I: To study the association of BMI and height with risk for glioma, meningioma and schwannoma in the HUNT study.

Paper II: To study BMI, height and smoking as potential risk factors for pituitary adenoma in the HUNT study.

Paper III: To assess whether BMI and height are associated with risk for different intracranial glioma subgroups, defined by the WHO 2007 glioma classification and a proxy for the WHO 2016 update, in the SSU study.

Paper IV: To confirm BMI as a risk factor for meningioma in a large adult cohort of women and men and assess the association of BMI and height with risk for intracranial glioma, pituitary adenoma and nerve sheath tumour, in the SSU study.
MATERIAL AND METHODS

ETHICS

This study was approved by the Regional Committee for Ethics in Medical Research (REK # 2011/428).

STUDY POPULATIONS

Papers I and II are based on data from the first Nord-Trøndelag Health Study (HUNT 1). HUNT 1 was performed from 1984 to 1986 as a general health study in the county of Nord-Trøndelag among adults 20 years of age and older. HUNT represents the largest Norwegian health survey and was primarily designed to study the prevalence of hypertension and diabetes as well as evaluate the quality of life in participants with hypertension, diabetes and tuberculosis (http://www.ntnu.no/hunt/hunt1). Among 85 100 eligible persons, 77 310 (90.8%) returned the first questionnaire that was mailed with the invitation to the health survey. Of those, 74 977 (88.1% of eligible persons) attended the subsequent physical examination that included standardized measurements of height and weight. Participants in the baseline examination also received a second questionnaire, which included questions about life-style factors and medical history and was to be returned in a pre-stamped envelope. Information on BMI was available in 74 339 participants, representing 87.4% of the eligible population. Details of the questionnaires can be found on the HUNT study’s website (www.ntnu.edu/hunt).

In paper I we further excluded participants with prevalent primary CNS tumours or missing follow-up data, resulting in a study population of 74 242 (87.4%) participants. For the analyses presented in paper II, an updated linkage to the Cancer Registry of Norway had been performed and we also excluded other cancer diagnoses. Therefore, our final study population consisted of 71 920 (84.5%) participants.

Papers III and IV are based on data from the Statens Skjermbildeundersøkelse (SSU). Since the late 1940s, Norway has had a mandatory screening program for tuberculosis conducted by the National Mass Radiography Service, which included a vaccination program, tuberculin tests and chest X-rays. The last nationwide screening was performed in 17 of the 19 counties between 1963 and 1975. A unique 11-digit ID number was used for identification of each Norwegian resident, and screening data were stored electronically. These included the body height and weight of participants as measured by trained
personnel. The screening program had an attendance rate of approximately 83% of the eligible population. Initially, the database consisted of 1,911,627 participants. We excluded 20,697 (1.1%) with prevalent cancer diagnoses (including benign and malignant CNS tumours), 5,868 (0.3%) with ongoing pregnancy, 23,206 (1.2%) aged 80 years or older, 3,713 (0.2%) aged < 14 years and 2,822 (0.1%) with missing data on BMI. Our study population then comprised 1,855,333 women and men between 14 and 80 years of age.

### STUDY FACTORS

#### DEPENDENT VARIABLES

Diagnosis of CNS tumours was based on a combination of topography and morphology codes [International Classification of Diseases, 7th Revision (ICD-7), and International Classification of Diseases for Oncology, third edition (ICD-O-3)].

In paper I, CNS tumours were included based on topography codes (ICD-O-3) C70 (meninges), C71 (brain), and C72 (spinal cord, cranial nerves and other parts of the CNS), and tumour subgroups were defined by morphology codes (ICD-O-3) 9380-9480 for glioma, 9440-9442 for glioblastoma, 9530-9539 for meningioma and 9560 for nerve sheath tumour.

In paper II, pituitary adenoma was defined by topography code C75 in combination with morphology codes 8140 and 8271 (ICD-O-3).

In paper III and IV, intracranial tumour location was defined by topography codes 193.0-193.2 and 195.3-195.5 (ICD-7). In paper III, the four most commonly diagnosed glioma subgroups were defined as the following: glioblastoma 9440-9442; astrocytoma 9381, 9384, 9400, 9401, 9410, 9411, 9420, 9421, 9424; oligodendroglioma 9450, 9451, 9460; and malignant glioma, not otherwise specified (NOS) 9380. In paper IV, tumour subgroups were defined by ICD-O-3 morphology code as follows: 9380-9480 for glioma, 9530-9539 for meningioma, 9540-9570 for nerve sheath tumour and 8140-8300 for pituitary adenoma.
INDEPENDENT VARIABLES

Age

In all four papers, participants’ age was defined as age in years at the time of baseline measurement of height and weight. In paper I, age was categorized as 20-29, 30-39, 40-49, 50-59, 60-69 and >70 years and included as a variable in the Cox regression analysis. In papers II, III and IV, age as a continuous variable was included in the Cox regression analysis as the underlying time variable. Furthermore, in paper III and IV, stratified analyses were performed for different categories of age (<30, 30-44, 45-59 and ≥60 years of age). Additionally, participants were categorized into four birth year cohorts: <1911; 1911-1925; 1926-1941; >1941.

BMI and height

Body height and weight were measured by trained personnel at the baseline examination in the HUNT and SSU study. BMI was calculated as weight divided by height squared (kg/m$^2$) and categorized as <20, 20-24.9, 25-29.9 or ≥30 kg/m$^2$. In paper I and II, BMI was also dichotomized at 25 kg/m$^2$. Overweight was defined as BMI 25-29.9 kg/m$^2$, obesity as BMI ≥30 kg/m$^2$, and underweight as BMI <20 kg/m$^2$; BMI 20-24.9 kg/m$^2$ was used as the reference category. Furthermore, BMI was included as a continuous variable in the Cox regression analysis, as well as per 5 kg/m$^2$ increase in BMI in papers III and IV.

Body height was categorized in quartiles for men and women and per 10 cm increase in height. Height was also tested as a continuous variable in the Cox regression analysis.

Physical activity, marital status, education, smoking, alcohol consumption, hypertension

In papers I and II, based on the HUNT database, several other potential confounding variables were included. Physical activity (walking, skiing, swimming or other sports) was assessed as frequency of the activity per week and categorized as never, 0-1 or ≥ 2 times per week. Marital status was divided into married, unmarried, widowed or divorced/separated. Level of education was categorized as <10, 10-12, or >12 years of school. Smoking status was categorized as current, former or never smoking and, in paper II, also assessed as accumulated number of pack-years of smoking. Alcohol consumption was categorized into five categories in paper I (0, 1-4, 5-10, >10 times during the last two weeks or total abstainer) and three categories in paper II (0, 1-4 or >4 times during the last two weeks).
Blood pressure was measured in mmHg at the baseline examination in HUNT. In paper II, hypertension, defined as being on anti-hypertensive drugs or as systolic blood pressure ≥140 mmHg or diastolic pressure ≥90 mmHg, was included in the analysis.

**LINKAGE TO THE CANCER REGISTRY OF NORWAY AND FOLLOW-UP**

The Cancer Registry of Norway, an institute of population-based cancer research, was established in 1951 and is one of the oldest national cancer registries in the world. Since then, reporting of cancer, including malignant and benign tumours of the CNS, has been mandatory for clinicians and pathology departments, and the registry has also had access to death certificates, hospital discharge summaries and radiotherapy treatment data. In 1961, a unique 11-digit ID number for every Norwegian resident was introduced, which has been universally used for identification since then. This number enabled linkage between the HUNT and SSU databases and incidence data from the Cancer Registry of Norway. Follow-up time was calculated as years from the date of baseline screening until the date of diagnosis of the dependent variable (tumour of the CNS, as defined per paper), any other cancer diagnosis (paper II – IV), date of emigration, date of death from any cause, or end of follow-up (December 15, 2008 for paper I; December 15, 2011 for papers II – IV), whichever occurred first.

**STATISTICAL ANALYSES**

In all four papers, the Cox proportional hazard regression model was used to assess the association between exposure variables and risk for the dependent variables (the different CNS tumour subgroups). Cox regression analysis is a well-established method for analysing data with survival time and censoring of follow-up, but it requires the hazard ratio to remain constant over time. This was tested by plotting the logarithm of the integrated hazards (log-log survival plots) and analysing Schoenfeld residuals.

In paper I, age- and sex-adjusted hazard ratios with 95% confidence intervals were obtained and further adjusted for potential confounding by physical activity, marital status, education, smoking and alcohol consumption. In paper II, age as the underlying time variable was used in the Cox regression model and adjusted for sex. Potential confounders were explored and retained in the model if they changed the modelled estimates by more than 10% or were known to be associated with obesity or smoking. Additionally, in paper II competing risk regression according to Fine and Gray's
proportional hazards model was used to analyze time to PA diagnosis with all-cause death as the competing event and age as the underlying time variable.\textsuperscript{102}

In papers III and IV, Cox proportional hazard regression, using attained age as the time axis, adjusted for birth cohort and sex, was used to calculate hazard ratios with 95\% confidence intervals. Furthermore, we performed stratified analyses by sex and different age groups. In all papers, we performed sensitivity analyses to minimize the likelihood of reverse causality by excluding participants with five years of follow-up or less. In papers III and IV, the difference between two HR estimates was assessed by testing interaction, as previously described.\textsuperscript{103} In paper III, power calculations for Cox regression models were performed for each tumour subgroup by utilizing the individual probability of failure, the standard deviation and the squared multiple correlation coefficients of height and BMI.\textsuperscript{104}

For all analyses, a two-tailed significance level of 0.05 was used. SPSS statistics software version 20.0 (IBM SPSS Inc., Chicago, IL) was used for statistical analysis in paper I, and STATA/SE statistics software Version 12.1 and 14.0 (StataCorp, 4905 Lakeway Dr, TX 77845, USA) for papers II – IV.
SYNOPSIS OF PRESENTED STUDIES

Paper I

Body mass index and the risk of meningioma, glioma and schwannoma in a large prospective cohort study (The HUNT study)

Background: Obesity increases the risk for a number of solid malignant tumours. However, it is not clear whether body mass index and height are associated with the risk of primary tumours of the central nervous system.

Methods: In a large population study (the HUNT study) of 74,242 participants in Norway, weight and height were measured. During follow-up, incident CNS tumours were identified by individual linkage to the Norwegian Cancer Registry. Sex- and age-adjusted and multivariable Cox regression analyses were used to evaluate BMI and height in relation to the risk of meningioma, glioma and schwannoma.

Results: A total of 138 meningiomas, 148 gliomas and 39 schwannomas occurred during 23.5 years (median, range 0-25) of follow-up. In obese women (BMI ≥30 kg/m²), meningioma risk was 68% higher (HR=1.68, 95% CI 0.97-2.92, p_trend=0.05) than in the reference group (BMI 20-24.9 kg/m²), whereas no association with obesity was observed in males. There was no association of BMI with glioma risk, but there was a negative association of overweight/obesity (BMI ≥25 kg/m²) with the risk of schwannoma (HR=0.48, 95% CI 0.23-0.99). However, the schwannoma analysis was based on small numbers. Height was not associated with the risk for any tumour subgroup.

Conclusion: These results suggest that BMI is positively associated with meningioma risk in women and possibly inversely associated with schwannoma risk.
Paper II

Smoking, obesity and the risk of pituitary adenoma: a large prospective cohort study (the HUNT study)

Background: The aetiology of pituitary adenoma is unclear. In this study, the association between smoking, obesity and the risk for pituitary adenoma was investigated.

Methods: In a large population study in Norway (the HUNT study) 71,920 participants were followed for a median of 26 years and PAs identified by linkage to the Cancer Registry of Norway. Using Cox regression analysis, the association between smoking, body mass index and the risk of PA was assessed.

Results: During 1,516,536 person-years of follow-up, 49 PAs were identified. Smoking status was negatively associated with the risk of PA compared to never smoking (HR 0.27; 95% CI 0.10-0.72), and more than 10 pack-years of smoking reduced the tumour risk by 76% (HR 0.24, 95% CI 0.07-0.82). Overweight and obesity were not associated with PA risk.

Conclusion: In this study, smoking significantly reduced the risk of PA, whereas overweight and obesity were not associated with PA risk.
The impact of body mass index and height on risk for glioblastoma and other glioma subgroups: a large prospective cohort study

Background: Glioma comprises a heterogeneous group of mostly malignant brain tumours, whereof glioblastoma (GBM) represents the largest and most lethal subgroup. Body height and body mass index (BMI) are risk factors for other cancers, but no previous study has examined anthropometric data in relation to different glioma subgroups.

Methods: This prospective cohort study includes 1.8 million Norwegian women and men between 14 and 80 years of age at baseline. Body weight and height were measured, and incident cases of glioma were identified by linkage to the Cancer Registry of Norway. Cox regression analyses were performed to evaluate risk for different glioma subgroups in relation to anthropometric measures.

Results: During 54 million person-years of follow-up, 4,382 gliomas were identified. Overweight and obesity were not associated with risk for any glioma subgroup. Height was positively associated with risk for GBM and all other glioma (HR per 10 cm increase: 1.24; 95% CI 1.17-1.31 and 1.18; 95% CI 1.09-1.29) but not with the proxy for IDH-mutant glioma (HR 1.09; 95% CI 0.98-1.21). In further subgroup analyses, the effect of height on glioma risk varied significantly, with positive associations for oligoastrocytoma (HR 1.74; 95% CI 1.20-2.53) and malignant glioma NOS (HR 1.42; 95% CI 1.16-1.76) but not for diffuse astrocytoma (WHO grade II and III) or oligodendroglioma.

Conclusion: This epidemiologic study confirms height as a risk factor for GBM and other subgroups of glioma. It further indicates that this association is not universal for glioma but may differ between different glioma subgroups.
Paper IV

Overweight, obesity and height as risk factors for glioma, meningioma, pituitary adenoma and nerve sheath tumours: Results from a large prospective cohort study

Background: In 2016, the International Agency for Research on Cancer announced that avoiding body fatness contributes to preventing meningioma occurrence but considered the available evidence for glioma inadequate.

Objectives: To confirm overweight and obesity as risk factors for meningioma; to assess whether body mass index or body height is associated with risk for intracranial glioma, pituitary adenoma or nerve sheath tumour.

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

Results: During 54 million person-years of follow-up, 4,382 gliomas, 3,335 meningiomas, 1,071 PAs and 759 NSTs were diagnosed. Obesity (BMI ≥ 30 kg/m²) was not associated with risk for glioma or meningioma 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/m²). For intracranial NSTs, obesity was associated with reduced tumour risk (HR 0.68; 95% CI 0.46-0.99). Height was associated with increased risk for all four tumour 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, while they seem to be associated with PA and NST risk.
Hazard ratios reported in observational studies may reflect a true effect of exposure on the development of disease but may also be influenced by different sources of bias. While study results may be explained by chance alone, which is difficult to control for, systematic errors always need to be considered in observational studies. The main sources of systematic bias in cohort studies are selection bias, information bias and confounding.

Selection bias may also have occurred if there was an underrepresentation of obese participants, which may represent an explanation of why the effect of BMI on meningioma risk may have been underestimated in paper IV.

Study participants with prevalent cancer or CNS tumour diagnosis were excluded from our study samples in papers II to IV. This was based on the hypothesis that the exposure variable BMI might be influenced by prevalent cancer as well as different cancer
treatment. Unfortunately, in paper I no information on other cancer or CNS tumour diagnosis prior to study baseline was available.

Another potential source of bias may have occurred due to missing data. In paper II, where the association between smoking status and risk for PA was assessed, information about smoking habits was based on responses on the second questionnaire which was handed out at the time of physical examination and should be returned by mail. However, the response rate to this second questionnaire was significantly lower compared to the first, and 17% of the study participants did not answer the question of smoking status. To maintain statistical power for the other main exposure variable (i.e. BMI) and assess if missing data were missing at random, we decided to include study participants lacking information about smoking status as a “missing” category.

Censoring of study participants is another source of bias if the association between exposure and disease in censored study participants differed from that in non-censored participants. This may be of particular importance in paper II, in which the influence of smoking on PA risk was assessed. Smoking is a known risk factor for development of cancer and cardio-vascular disease and is associated with increased mortality.\textsuperscript{106,107} Smoking may therefore lead to premature censoring, preventing the development of PA. The observed incidence of PA in smokers may therefore be falsely low, and smoking may seem to be protective for PA as found in our study. In order to reduce the risk of this bias, we implemented a competing risk model with all-cause death as the competing event. Ideally, we should have performed a competing risk model for smoking-related death in particular, but cause of death was unfortunately not available in our study.

**INFORMATION BIAS**

Systematic differences in data acquisition may affect both independent and dependent variables. In our study, body height and weight were measured at baseline by trained personnel, reducing the likelihood of information bias in contrast to self-reported anthropometric measures. Also, the prospective design of cohort studies prevents the likelihood of recall bias, a common problem in case-control studies in which cases may remember exposures differently than controls.

An important assumption of cohort studies especially with long-term follow-up is that exposure is constant over time. While height may only vary little over time, BMI has been shown to increase with age,\textsuperscript{108} and an association of small effect size between
overweight or obesity and CNS tumour risk may have been underestimated in our study. Obviously, this also applies for exposures such as smoking, as participants may have started or stopped smoking during follow-up. This change in exposure during follow-up may have had an impact on the risk associations reported in our study.

Diagnoses of CNS tumours were obtained from the Cancer Registry of Norway, previously shown to have high-quality incidence data, including completeness and validity.\textsuperscript{109} However, the incidence of CNS tumours has been increasing over the last few decades, mainly due to the technical advances in diagnostic imaging as well as its increased accessibility, leading to a growing number of incidentally found tumours and a younger age at the time of diagnosis.\textsuperscript{1,110,111} To take this into account, we analysed data of the SSU database stratified for birth cohorts.

**CONFOUNDING**

Confounding occurs when a variable is associated with the dependent variable (i.e. CNS tumour subgroup) as well as the independent variable of interest (e.g. BMI or height). Adjustment for confounders can only be performed if the association with the dependent variable is known and the confounding variable is adequately measured. BMI, for example, may be associated with multiple other factors, such as socioeconomic status, diet, metabolic factors, age and physical activity. Although many different factors have been studied in association with CNS tumour risk, the only established risk factors so far are age, sex, genetic syndromes and ionizing radiation.\textsuperscript{14,40,112-114} Thus, epidemiologic studies should at least be controlled for age and sex as known confounders. In Norway, the most common source of ionizing radiation is radiotherapy for cancer. Therefore, we excluded subjects from our study cohorts with a prevalent cancer diagnosis, and study participants were censored at the time of any cancer diagnosis. Unfortunately, we could not control our study cohorts for genetic syndromes as a cause of CNS tumours. However, CNS tumours associated with genetic syndromes represent only a small percentage of all CNS tumours, while the majority occur sporadically.\textsuperscript{1,8} It is therefore unlikely that their inclusion would alter study estimates significantly. Furthermore, in the SSU study we only included intracranial NSTs (the vast majority of which are vestibular schwannomas), which at least might reduce the risk of including subjects with neurofibromatosis 1, the most common of the familial tumour syndromes.\textsuperscript{19}
In paper II, smoking was associated with a reduced risk of PA, and smoking has also been reported to be negatively associated with BMI.\textsuperscript{115} The association of BMI with CNS tumour risk may therefore be confounded by smoking. Unfortunately, in the SSU study no information about smoking, other lifestyle factors or metabolic measures was available. This obviously represents the biggest limitation of the SSU study.

Socioeconomic status as potential confounder requires some consideration. Both height and weight are associated with socioeconomic status, but the direction of causality is less certain. Taller stature and weight within the normal range are related to higher standards of nutrition which often comes with higher socioeconomic status.\textsuperscript{116-119} However, there is also evidence in the opposite direction in that higher socioeconomic status is a consequence of tallness and lower BMI.\textsuperscript{120,121} This hypothesis has recently been supported by a large Mendelian randomization study demonstrating that different genotypes determining height and weight significantly influenced socioeconomic status later in life. This study demonstrated that overweight or obese study participants (as defined by their genotype) were at a disadvantage, while taller study participants, especially men, had an increased socioeconomic status later in life.\textsuperscript{122}

In the HUNT study (papers I and II), education as a proxy for socioeconomic status was included as a potential confounder in the analyses, but it did not influence the association of other variables with CNS tumour risk. In the SSU study (papers III and IV), socioeconomic status was not assessed and could not be controlled for as a potential confounder.

Due to the association between height, BMI and socioeconomic status, ideally all three of them should be included in epidemiologic studies. However, studies that have assessed anthropometric data and included socioeconomic status as a potential confounder have not reported an association between socioeconomic status and CNS tumour risk or confounding of anthropometric variables.\textsuperscript{74,93,98,123-125} On the other hand, studies that have reported an association between socioeconomic status and CNS tumour risk have generally not included height or BMI as potential confounders in the analyses.\textsuperscript{53,126-130} Therefore, it cannot be excluded that the effects seen in those studies are in fact driven by anthropometric measures rather than socioeconomic status itself.

The role of socioeconomic status as potential risk factor for different CNS tumour subgroups would be strengthened if the association were consistent, had a dose-response profile and a convincing effect size. Recently, a large population-based cohort
study reported on socioeconomic status and risk for glioma, meningioma and vestibular schwannoma.\textsuperscript{126} Although this study suggested some evidence for an association between different measures of socioeconomic status and CNS tumour risk, there was some inconsistency in the reported association between CNS tumour subgroups and the effect size was rather small. Discrepancies between socioeconomic categories and between women and men also raised some doubt of a strong association with CNS tumour risk \textit{per se}. More importantly, height and BMI were not included in the statistical model.

\section*{POWER}

A recurring challenge of epidemiologic studies on CNS tumours is the low incidence rate, especially if different tumour subgroups are considered separately. Small sample size or insufficient follow-up may lead to underpowered studies and type II errors. In paper I and II, the numbers of NSTs and PAs were too small for a more detailed analysis of height and BMI categories. Additionally, in the most common tumour subgroups of meningioma and glioma, the number of cases was too low to perform Cox regression analyses including multiple variables and stratification for sex. Negative results in papers I and II may therefore just indicate a lack of power and not necessarily an absence of association. In paper III, subgroups of glioma were analysed and power calculations performed \textit{a priori}. Dependent on the expected effect size, the power of subgroup analyses for oligodendroglioma and malignant glioma NOS was low, and a type II error for the association of height with oligodendroglioma cannot be excluded. For the other glioma subgroups, power was high, and therefore a type II error as an explanation for the absence of association is unlikely. In paper IV, there was sufficient power for all four CNS tumour subgroups to rule out a type II error with confidence.

\section*{DEFINITION OF INDEPENDENT VARIABLES}

In our study, we aimed to assess the relation between anthropometric measures and risk for different CNS tumours. The easiest and most reliable way to obtain anthropometric data is to measure body height and weight. Measured adult height directly reflects tallness and changes minimally during lifetime; body mass index, defined as the quotient of body mass and height squared, is a common marker for adiposity, and overweight and obesity are defined as BMI of 25-29.9 kg/m\textsuperscript{2} and >30 kg/m\textsuperscript{2}, respectively.\textsuperscript{131} Even though BMI is a useful measure of adiposity, it imperfectly reflects body composition, as BMI can
be increased due to adipose tissue but also lean tissue mass. Other, more direct measures of adiposity such as waist circumference or waist-to-hip ratio were unfortunately not available in our study.

DEFINITION OF DEPENDENT VARIABLES

Information about outcome (i.e. CNS tumour diagnosis) was obtained by linkage of the cohort studies (i.e. HUNT and SSU) to the Cancer Registry of Norway. The Cancer Registry of Norway was established in 1951, and there has been mandatory reporting of cancer, including malignant and benign CNS tumours, for clinicians, general practitioners, laboratories and hospitals. For nearly a century, CNS tumours have been classified by histology, based on the concept of microscopic similarities in tumour cell origin and differentiation. In 1979, the WHO introduced a grading system for CNS tumours, where histological grade should reflect the biological behaviour and prognosis of neoplasms. There are four WHO grades (i.e. I to IV), which are thought to be a “malignancy scale”, used for a wide variety of neoplasms. CNS tumours of WHO grade I usually represent neoplasms with low proliferative activity and the potential for cure if resected completely. WHO grade II lesions have an infiltrative growth pattern and have a tendency for recurrence as well as malignant transformation, even if they initially have low proliferative activity. WHO grade III lesions are considered malignant, and histologic features include nuclear atypia and increased mitotic activity. Grade IV lesions are malignant neoplasms with poor prognosis and cytological features of malignancy, such as high mitotic index, nuclear atypia, necrosis and microvascular proliferation. WHO grade III and IV tumours are usually treated with adjuvant radiotherapy and/or chemotherapy.

Different classification of CNS tumour entities and subgroups obviously has some implications for our study. While the large majority of meningiomas, PAs and NSTs are benign lesions, glioma constitutes a much more heterogeneous group of neoplasms. Therefore, in paper III we assessed height and BMI in relation to different glioma subgroups, hypothesizing that there might be differences in tumour subgroups due to their diverse biological behaviour. However, defining different glioma subgroups may be a matter of debate. Until 2016, the definition of glioma was mainly based on concepts of histogenesis, including microscopic features, immunostaining and ultrastructure characterization. Thus, tumours with an astrocytic phenotype were grouped separately
from those with an oligodendroglial phenotype, and mixed glioma or oligoastrocytoma constituted a distinct diagnostic category.\textsuperscript{10} The 2016 update of the CNS WHO classification system refined the definition of glioma subgroups to include genotypic parameters such as IDH mutation or 1p/19q codeletion status, leading to a more objective definition of diffuse glioma subgroups and regrouping astrocytomas and oligodendrogliomas with regard to different growth patterns and prognosis.\textsuperscript{10} Therefore, applying the “old” classification to our study might be interesting but not necessarily applicable to future glioma categories. Unfortunately, this updated classification system could not be applied to our study directly, as this would have required a pathological review of all cases which we considered not to be feasible Therefore, we created proxies for IDH mutation status positive and negative glioma subgroups in paper III, obviously with a chance of inducing selection bias.

**HEIGHT AND TUMOUR RISK**

Results from the SSU study indicate that height is associated with risk for glioma, meningioma, PA and NST. Furthermore, we found that height is not universally associated with all glioma subgroups. In the HUNT study, we did not find significant associations between height and risk for CNS tumour subgroups. However, the results for glioma in relation to height in HUNT were similar to those from the SSU study (HR 1.23; 95% CI 0.96-1.59 per 10 cm increase in height for women and men in the HUNT study and HR 1.22; 95% CI 1.17-1.28 in the SSU study), although the association in HUNT was not significant. The smaller sample size in HUNT may have prevented us from observing a significant association and may not represent a true absence of an association. For meningioma and NSTs, the results were less consistent. In the HUNT study no association was found for height with NSTs (HR 1.02; 95% CI 0.62-1.67 per 10 cm increase in height), nor with meningioma (HR 0.93; 95% CI 0.70-1.24). These associations remained unchanged when socioeconomic status was included in the statistical model. Interestingly, in the SSU study the association of height with risk for meningioma or NST was less pronounced than for glioma or PA. Thus, the negative results from the HUNT study may be due to the smaller sample size, but the strength of the association also seems less significant. In contrast, even if the association between height and PA was not significant in HUNT, the point estimate of the HR was similar to what we reported in the SSU study [HUNT HR 1.18 (95% CI 0.73-1.88) per 10 cm increase in height; SSU HR 1.29 (95% CI 1.17-1.42)]. Therefore,
the association between height and risk for glioma and PA therefore seems more robust than for meningioma and NSTs.

Our findings of a positive association between height and glioma risk are in congruence with other studies, while reports on meningioma risk have been more inconsistent. So far, knowledge about height and risk for PA or NST has been scarce, and our results from the SSU study are, to our knowledge, the first large-scale data for those rarer tumour subgroups in relation to height. We could further demonstrate consistency of the association between height and risk for different tumour subgroups across all age groups, reducing the likelihood of measuring the effect of different birth cohorts, which otherwise could have biased the results.

**BMI AND TUMOUR RISK**

Our results from the HUNT study indicate that body fatness (i.e. overweight and obesity) is a risk factor for meningioma, while it seems to be protective against NST. No significant association was found for glioma or PA. However, due to small numbers, no definite conclusions could be drawn regarding body fatness and the risk for different CNS tumour subgroups, and, although present, the effect of body fatness on meningioma risk seemed not to be very robust and was seen only for women and not men.

We therefore assessed the association between anthropometric measures and CNS tumour risk in the much larger SSU study to obtain more robust results regarding body fatness as a risk factor for meningioma and to clarify the relation to other tumour subgroups. Surprisingly, the SSU study did not confirm the association between overweight or obesity and meningioma risk, although the study had enough power to detect even a small effect size. Furthermore, the SSU study showed an inverse association between body fatness and NST, as indicated by the HUNT study, and suggested a positive association with risk for PA. Additionally, it could be confirmed that glioma risk, overall and in different subgroups of glioma, was not associated with body mass index in either direction.

Our study results for body fatness and meningioma risk stand in contrast to the recent announcement of the IARC, claiming a protective effect for avoidance of body fatness in regard to meningioma risk. This recommendation was based on the best available evidence, recently summarized in three meta-analyses, reporting a positive association between overweight or obesity and meningioma risk, which also included
results from our first paper based on the HUNT study.\textsuperscript{137-139} Obviously, the results of all three meta-analyses are largely based on the same original studies, whose methodology should be assessed more closely. Reports on meningioma risk and body fatness in men are scarce, and no significant association has been proposed by any prospective cohort study. Thus, the results from the meta-analyses in regard to meningioma risk in men are predominantly driven by one large case-control study, relying on retrospectively self-reported body weight.\textsuperscript{140} 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.\textsuperscript{74,100,135} In contrast, 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.\textsuperscript{124,141} Our data from the SSU study exceed the meta-analyses in size and power.\textsuperscript{137-139} We were further able to perform robust subgroup analyses for women and men as well as different age groups without finding convincing evidence of a strong association between overweight or obesity and risk for meningioma. Our findings therefore raise doubt that overweight and obesity per se are important risk factors for meningioma. However, an underestimation of the effect of overweight and obesity on meningioma risk due to the long follow-up period in our study may be considered. Still, this seems unlikely, as an association of the rarer CNS tumour subgroups PA and NST with body fatness could be demonstrated and remained stable in sensitivity analyses, in which the first 5 years of follow-up were excluded.

In our study, overweight and obesity were not associated with glioma risk, either overall or in different glioma subgroups. This is in keeping with the majority of previous studies\textsuperscript{74,99,124,134} and a recent meta-analysis.\textsuperscript{139} However, our results are in contrast to the study by Moore et al. in which a more than 3-fold increase of glioma and GBM risk in study participants who were obese at the age of 18 years was reported.\textsuperscript{98} While the results of their study may be prone to recall bias as participants between 50 and 70 years of age recalled their BMI at younger age, the SSU study prospectively included BMI measures of young participants. Further, the association reported by Moore et al. did not show a dose-response relation and was based on small numbers.\textsuperscript{98} Our study may therefore contribute to clarify the role of body fatness for the risk of glioma as the most recent IARC report still concluded that there was inadequate evidence to allow conclusions with regard to the presence or absence of a glioma-preventive effect of reducing body fatness.\textsuperscript{136}
Associations between BMI and risk for PA or NST have so far hardly been assessed. In the HUNT study, the number of PAs and NSTs was small, and, although a trend for an inverse association between body fatness and NST was indicated, results were not significant. The SSU study for the first time provides data on a reasonable number of PAs and NSTs to assess the associations with body fatness in a prospective study design. Whereas body fatness seemed to increase the risk for PA in women and men, it decreased the risk for NST. The negative association with NST has been indicated by one previous study, but that study was limited in size and power. However, in both tumour subgroups of PA and NST, reverse causality may have biased the results. In PAs, initially unrecognized hormone-producing tumours may influence body mass index, thus inverting cause and effect. In NSTs, the vast majority of which are represented by vestibular schwannoma, vertigo and tinnitus are the most common symptoms. Secondary weight loss due to those symptoms may therefore occur before the diagnosis of NST is made. Therefore, reverse causality may be considered as an explanation for the effects seen. To reduce the chance of bias, we excluded all participants with follow-up of less than 5 years, which we assumed to be a reasonable time from the onset of symptoms to the diagnosis of a tumour. However, the associations remained unchanged, thus minimizing the likelihood of reverse causality as an explanation.

POTENTIAL MECHANISMS

The biological mechanisms that may underlie the differing associations between height and CNS tumour subgroups are unknown. However, one hypothesis suggests the insulin-like growth factor (IGF) pathway as a potential link between height and CNS tumour risk. IGFs are important determinants of body height attained during childhood and adolescence and have previously been linked to cancer development. Growth hormone (GH) is a key factor in IGF expression in postnatal life and is influenced by the supply of dietary energy and protein. Circulating levels of IGFs are highest during puberty and decrease rapidly in the third decade of life but seem to stay consistently higher in taller adults. Insufficiency in GH and IGFs during childhood and adolescence leads to reductions in body height and bone mineral density but increases body fat mass.

Expression of insulin-like growth factor binding protein-2 (IGFBP-2) in glial cells is important for brain development in utero but decreases significantly after birth. IGFBP-2 has been shown to be overexpressed in over 80% of GBM and to be one of the
strongest biomarkers of aggressive behaviour.\textsuperscript{148,149} Furthermore, overexpression of IGF-I and IGF-II mRNA transcripts was found in meningioma,\textsuperscript{150} and a positive association between serum IGF-I and IGFBP-3 concentrations and intracranial schwannoma risk has been reported.\textsuperscript{151} Recent data from animal studies indicate that IGFBP-2 inhibition leads to a significant decrease in glioma progression and prolonged survival and may therefore represent a target for treatment.\textsuperscript{149} In contrast, IGFBP-2 has largely been undetectable in low-grade astrocytic and oligodendrogliomas,\textsuperscript{152} while up-regulation of IGFBP-2 was found to be a consistent and distinct gene expression change in different classes of gliomas.\textsuperscript{153} Furthermore, IGFBP-2 overexpression appeared when tumour progression in astrocytomas and oligodendrogliomas occurred and was shown to be a key oncogenic signal in tumourigenesis.\textsuperscript{154} It has also 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 risk for intracranial tumours.\textsuperscript{134}

**PUBLIC HEALTH IMPLICATIONS**

According to the WHO, disease prevention is the most cost-effective long-term strategy for cancer control. Already in 2002, the IARC has recommended avoidance of body fatness for reduction of the incidence of colon, breast (in postmenopausal women), endometrium, and kidney cancer (renal cell carcinoma) as well as adenocarcinoma of the oesophagus.\textsuperscript{86} In 2016, the IARC identified an additional eight cancers for which sufficient evidence suggested that the absence of body fatness lowered cancer risk. For the first time, this also included a tumour of the CNS, meningioma.\textsuperscript{136} The evidence of an association between BMI and risk for the most common malignant tumour of the CNS, glioma, was considered inadequate.\textsuperscript{136} Our first paper, derived from the HUNT database, has contributed to this recommendation, as we reported an association between meningioma risk and body fatness,\textsuperscript{155} and our paper was part of the meta-analyses, which have reported a positive association between overweight, obesity and meningioma risk.\textsuperscript{137-139} However, in contrast to our expectations, the results of the SSU study could not confirm the positive association between meningioma risk and body fatness (paper IV). Although the limitations of this paper have been discussed above, including the main criticism of lack of potential confounding factors in the SSU study, its prospective design, measurement of BMI at baseline and large size raise doubt of the recommendation given by the IARC. In fact, the size of the SSU study exceeds the size of the meta-analyses, and including it in a future meta-analysis would most likely lead to a lack of a significant
association between overweight or obesity and meningioma risk. This may influence future recommendations by the IARC.

The association between height and CNS tumour risk cannot easily be applied to a public health perspective. Height is predetermined genetically but also influenced by nutrition during adolescence. So far, little is known about possible pathomechanisms. Therefore, there is no practical implication for this finding at presence. It remains to be shown whether there is a future role for identifying high-risk groups for development of CNS tumours by combining several factors that might have the potential for preventive measures. Thus, understanding the aetiology of different CNS tumour subgroups is important for estimating future health impact as well as the effects of preventive measures.

**FUTURE PERSPECTIVES**

Our study has contributed to elucidating the association between height, BMI and risk for different CNS tumour subgroups. We could not confirm a strong association between risk for meningioma and body fatness as indicated by other studies. This finding requires further evaluation, as BMI may be a surrogate or a component of a more complex association involving metabolic factors, such as diabetes mellitus, serum lipid levels or hypertension. Cohort studies like the Cohort of Norway (CONOR), including data on metabolic factors will give us the opportunity to address this question in more detail. Furthermore, the rather new findings of a positive association between BMI and PA risk and an inverse association between BMI and NST risk require confirmation as well as other approaches to understand potential biological mechanisms.

So far, we have assessed the role of anthropometric factors in relation to CNS tumour risk. However, little is known about the prognostic impact of overweight and obesity in relation to CNS tumour risk. There is some evidence that overweight and obese people have a significantly increased risk for cancer death. However, to our knowledge, this has not been assessed for CNS tumour subgroups. The SSU database will give us the opportunity to examine this at least for large CNS tumour subgroups with high mortality, such as GBM.
CONCLUSION

This observational study, utilizing data from two large prospective, population-based cohorts, demonstrates the differences of height and body fatness in relation to different CNS tumour subgroups. Height seemed to be universally associated with the four largest CNS tumour subgroups of glioma, meningioma, pituitary adenoma and nerve sheath tumour. However, in analyses of different glioma subgroups, this association was more pronounced for the more malignant gliomas. Body fatness was not associated with glioma, and the association with meningioma was inconsistent. Increased BMI seemed to be protective against NST but increased risk for PA.
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