Original Article

Blood pressure and other metabolic syndrome factors and risk of brain tumour in the large population-based Me-Can cohort study

Michael Edlinger[a], Susanne Strohmaier[a], Håkan Jonsson[b], Tone Bjørge[c,d], Jonas Manjer[e], Wegene T. Borena[a], Christel Häggström[f], Anders Engeland[c,d], Steinar Tretli[g], Hans Concin[h], Gabriele Nagel[i], Randi Selmer[d], Dorthe Johansen[e], Tanja Stocks[f], Göran Hallmans[j], Pär Stattin[f,k], and Hanno Ulmer[a]

Objectives: Brain tumour has few established determinants. We assessed to which extent risk of brain tumour was related to metabolic syndrome factors in adults.

Methods: In the Me-Can project, 580 000 individuals from Sweden, Austria, and Norway were followed for a median of 10 years after baseline measurement. Data on brain tumours were obtained from national cancer registries. The factors of metabolic syndrome (BMI, SBP and DBP, and blood levels of glucose, cholesterol, and triglycerides), separately and combined, were analysed in quintiles and for transformed *z*-scores (mean transformed to 0 and standard deviation to 1). Cox proportional hazards multivariate regression models were used, with corrections for measurement error.

Results: During follow-up, 1312 primary brain tumours were diagnosed, predominantly meningioma ($n = 348$) and high-grade glioma ($n = 436$). For meningioma, the hazard ratio was increased for *z*-scores of SBP [hazard ratio = 1.27 per unit standard deviation, 95% confidence interval (CI) 1.03–1.57], of DBP (hazard ratio = 1.29, 95% CI 1.04–1.58), and of the combined metabolic syndrome score (hazard ratio = 1.31, 95% CI 1.11–1.54). An increased risk of high-grade glioma was found for DBP (hazard ratio = 1.23, 95% CI 1.01–1.50) and triglycerides (hazard ratio = 1.35, 95% CI 1.05–1.72). For both meningioma and high-grade glioma, the risk was more than double in the fifth quintiles of DBP compared to the lowest quintile. For meningioma this risk was even larger for SBP.

Conclusion: Increased blood pressure was associated with risk of brain tumours, especially of meningiomas.

Keywords: blood pressure, cohort study, epidemiology, high-grade glioma, meningioma, metabolic syndrome, primary brain tumour, risk factors

Abbreviations: CI, confidence interval; IQR, interquartile range; Me-Can, Metabolic syndrome and Cancer Project; MetS, metabolic syndrome; RDR, regression dilution ratio

INTRODUCTION

Primary brain and central nervous system tumours have an incidence of about 19 per 100 000 person-years in the USA. The most common types are meningiomas and gliomas, which each account for approximately one-third of all brain tumours [1]. The prospects are poor for patients with brain cancer, with 5-year survival rates of less than a third [2]. There are indications that the incidence of glioma and meningioma has increased in the past few decades [3], although part of this trend might be explained by changes in diagnostic procedures and medical care facilities. It is also unclear to what extent the few available data for international comparisons of brain tumour incidence are distorted by variations in diagnostic and reporting practices [4].

Brain tumour has few established determinants. To date, there are little data on the relationship between factors in metabolic syndrome (MetS) and risk of these tumours. One study found a significant association between blood glucose and incident brain cancer among men: a reduced risk with increasing levels of glucose [5]. In other studies investigating glucose or diabetes as a risk factor of brain tumour, the results are inconclusive [6–10]. Results for

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[a]Department of Medical Statistics, Informatics and Health Economics, Medical University Innsbruck, Innsbruck, Austria, [b]Department of Radiation Sciences, Oncology, Umeå University, Umeå, Sweden, [c]Department of Public Health and Primary Healthcare, University of Bergen, Bergen, [d]Norwegian Institute of Public Health, Bergen, Norway, [e]Department of Surgery, Skåne University Hospital Malmö and Lund University, Malmö, [f]Department of Surgical and Perioperative Sciences, Urology and Andrology, Umeå University, Umeå, Sweden, [g]Cancer Registry of Norway, Institute of Population-based Cancer Research, Oslo, Norway, [h]Agency for Preventive and Social Medicine, Bregenz, Austria, [i]Institute of Epidemiology, Ulm University, Ulm, Germany, [j]Department of Public Health and Clinical Medicine, Nutritional Research, Umeå University, Umeå, Sweden and [k]Department of Surgery, Urology Service, Memorial Sloan-Kettering Cancer Center, New York, New York, USA

Correspondence to Hanno Ulmer, Department of Medical Statistics, Informatics and Health Economics, Medical University Innsbruck, Schöpfstraße 41, 6020 Innsbruck, Austria. Tel: +43 512 9003 70900; fax: +43 512 9003 73922; e-mail: Hanno.Ulmer@i-med.ac.at

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overweight and hypertension have also been ambiguous [10–15]. However, this may be due to methodological problems such as case–control design and restricted numbers of cancer events. We had sound data available to study the effects of factors in MetS and the risk of brain tumour. In addition, the data allowed, to our knowledge for the first time, investigation of the combined effects of MetS factors.

Metabolic syndrome is estimated to have a prevalence of about 15% among nondiabetic adult Europeans [16], and the occurrence of some of the factors has been increasing [17], compatible with the apparent increases in incidence of glioma and meningioma.

In this large, population-based cohort study of almost 580 000 adults we aimed to investigate to what extent MetS factors are related to risk of primary brain tumours.

METHODS

Study population

The study group consisted of participants in the Metabolic Syndrome and Cancer Project (Me-Can), which has been described before [18]. In brief, information was gathered from 578 462 participants, ranging from 15 to 99 years of age at baseline (between 1972 and 2005), in seven population-based cohorts in Austria, Norway, and Sweden. Data were collected on height, weight, SBP and DBP, and circulating levels of glucose, total cholesterol, and triglycerides, as well as on fasting time (less than 4 h, 4–8 h, or more than 8 h) and smoking status (never, former, or current smoker). For this and other studies in Me-Can, each individual's baseline data were taken from the first (or only) health examination with complete or near-complete data. The current study differs from the others in the Me-Can project in that it includes benign as well as malignant brain tumours. Nationwide cancer and cause-of-death registries were used to follow-up participants. The research ethical committees in the respective countries gave their approval of the project.

Statistical analysis

The starting point of the follow-up period for analysis was set to 1 year after baseline, to reduce the possibility of reverse causation. For blood pressure we also performed sensitivity analyses by disregarding the first 5 years after baseline. The study endpoint was diagnosis of the first primary brain tumour. Follow-up ended at diagnosis of first cancer or brain tumour, emigration, death, or the end of the study period (31 December 2003 in the Austrian, 2005 in the Norwegian, and 2006 in the Swedish cohorts), whichever came first.

Cox proportional hazards regression was used to estimate hazard ratios and the accompanying 95% confidence intervals (CIs), with age as the time variable and models stratified by cohort. This stratification was especially done to account for differences in measurement procedures between cohorts. The proportionality assumption was assessed by plotting the estimated hazards on a log scale; no important deviations were found. All models were adjusted for sex, birth year (in decades), baseline age, and smoking status. For the quintiles analyses, the cut-points were determined sex-specifically within the cohorts, so for each sex and cohort combination a quintile distribution was established. For glucose, cholesterol, and triglycerides the cut-points were also determined within categories of fasting time. The lowest quintile of the exposure variable was used as the reference. In the quintiles analyses an extra adjustment was made for BMI. To allow the determinants to be compared on the same scale, the exposure variables were additionally transformed to standardized z-scores with a mean of 0 and a standard deviation of 1, when glucose and triglycerides were first transformed with natural logarithm because of their skewed distributions. A combined MetS score was constructed by adding the separate z-scores (with the mean of SBP and DBP transformed to one standardized z-score) and then standardizing the sum. Standardization was performed separately within each of the sexes and cohorts, and glucose, cholesterol, triglycerides, and MetS score were also standardized within the fasting time categories. In the z-score analyses, we also constructed extended models adjusting for the same variables as in the basic models but also for the other metabolic variables.

Exposure measurements are subject to measurement error and within-person variability, which may lead to a regression dilution bias of risk associations. We used the repeated measurements available for 133 820 of the participants to estimate regression dilution ratios [19,20] or regression calibration [21], both based on linear mixed-effect models. The regression dilution ratio method was applied when only one of the covariates in the model was subject to variability. When several covariates were corrected for random error, the calibration method was used.

The statistical analyses were performed with Stata/MP 10.1, except that the estimates necessary for random error correction were calculated with R 2.7.2.

RESULTS

The median age at baseline was 41 years [inter-quartile range (IQR) 39–49 years]. More than half of the participants were current or former smokers, nearly half were overweight (BMI $\geq$25 kg/m^2), and nearly a third had hypertension (Table 1). The median follow-up time was 9.6 years (IQR 6.9–14.3 years), totalling 6 789 618 person-years in all. During follow-up 1312 primary brain tumours were diagnosed at a median age of 56 years (IQR 47–65 years). In total, a third of the cases were diagnosed as high-grade glioma and 8% as low-grade glioma. In the Swedish and Norwegian cohorts, where the diagnostic coding was available, meningioma constituted 29% of all brain tumours (Table 2).

In the quintiles analysis, BMI, cholesterol, and triglycerides were not related to brain tumours (Table 3). For glucose, the fifth quintile, compared to the reference, showed a risk reduction of a half. In contrast, for blood pressure the highest quintile was associated with respective risk increases of 45% for SBP and 84% for DBP. Although the results for the other quintiles of DBP were not statistically significant, the risk estimates did rise with every next quintile.

When the meningiomas and gliomas were analysed separately, there were clear associations with blood pressure for meningioma and for high-grade glioma (Table 4).

TABLE 1. Baseline characteristics of the study participants

	Number of participants	Follow-up (person-years)
Cohort		
Oslo study I (Norway 1972–2005)	16 768 (3%)	443 687
Norwegian Counties Study (Norway 1974–2005)	51 033 (9%)	1 351 108
Cohort of Norway (Norway 1995–2005)	109 773 (19%)	774 984
Age 40 Programme (Norway 1994–2005)	128 812 (22%)	1 081 685
Vorarlberg Health Monitoring and Prevention Programme (Austria 1988–2003)	159 884 (28%)	1 659 511
Västerbotten Intervention Project (Sweden 1985–2006)	79 446 (14%)	742 718
Malmö Preventive Project (Sweden 1974–2006)	32 746 (6%)	735 925
Sex		
Female	288 675 (50%)	3 177 185
Male	289 787 (50%)	3 612 433
Year of birth		
1929 or earlier	67 036 (12%)	1 067 617
1930–1939	95 042 (16%)	1 701 132
1940–1949	89 705 (16%)	1 179 251
1950–1959	221 914 (38%)	1 997 014
1960 or later	104 765 (18%)	844 603
Age at baseline (years)		
≤29	60 311 (10%)	736 220
30–39	108 501 (19%)	1 449 979
40–49	273 782 (47%)	3 317 789
50–59	73 459 (13%)	766 589
60–69	41 550 (7%)	371 990
≥70	20 859 (4%)	147 052
Smoking status		
Never	258 212 (45%)	2 889 650
Former	158 592 (27%)	1 732 316
Current	160 097 (28%)	2 149 053
Unknown	1561 (0%)	18 599
BMI (kg/m^2)		
<25	301 604 (52%)	3 747 155
25-<30	210 619 (36%)	2 385 080
≥30	66 239 (11%)	657 382
Hypertension (SBP ≥140 and/or DBP ≥90 mmHg)		
No	392 306 (68%)	4 455 210
Yes	185 255 (32%)	2 324 130
Unknown	901 (0%)	10 277

For patients in the highest quintile of SBP, risk of meningioma was increased four-fold, compared to the lowest quintile, and intermediate quintiles had lesser but still large increases. Patients in the highest quintile of DBP had more than double increased risks of both meningioma and high-grade glioma. Other quintiles of DBP also had doubled risks of high-grade glioma. Although not statistically significant, the risk estimate for high-grade glioma was reduced in the fifth quintile of glucose and there was a striking contrast in estimates between the second and fifth quintiles of triglycerides (hazard ratio = 0.53, 95% CI 0.25–1.11 versus hazard ratio = 1.48, 95% CI 0.75–2.91). For low-grade glioma we did not observe clear associations with any of the factors of metabolic syndrome.

TABLE 2. Follow-up data on duration and on brain tumour types of the study participants

	Number of subjects	Follow-up (person-years)
Follow-up (years)		
<5	78 930 (14%)	262 592
5-<10	236 630 (41%)	1 859 150
10-<15	139 872 (24%)	1 709 023
15-<25	55 637 (10%)	980 788
≥25	67 393 (12%)	1 978 065
Type of primary brain tumour (ICD-7 code 193)		
Austrian cohort[a]		
Low-grade glioma	23 (19%)	133
High-grade glioma	69 (58%)	467
Other	27 (23%)	151
All brain tumours	119 (100%)	750
Norwegian and Swedish cohorts		
Meningioma	348 (29%)	3938
Low-grade glioma	86 (7%)	746
High-grade glioma	367 (31%)	4375
Other	392 (33%)	3939
All brain tumours	1193 (100%)	12 999

[a]No information on meningioma available in the Austrian cohort.

In the risk analysis based on *z*-scores, increased DBP was related to a higher risk of all brain tumours (Table 5). This positive relationship was strongest for meningioma, with a hazard ratio of 1.29 per standard deviation unit in the extended model (95% CI 1.04–1.58). The risk estimate was similar for SBP and meningioma (hazard ratio = 1.27 per unit, 95% CI 1.03–1.57). Two other associations with meningioma risk, of BMI and glucose, were significant in the basic models, but these disappeared after adjustment for additional factors in the extended models. For the total MetS score we found an increased risk of meningioma with a hazard ratio of 1.31 per unit (95% CI 1.11–1.54). High levels of triglycerides was associated with an increased risk of high-grade glioma, which remained significant after

TABLE 3. Risk of incident brain tumour for metabolic factors (quintiles)

		All brain tumours			
Exposure[a]	Q	Mean (SD)	No. of participants	HR[b]	95% CI
BMI (kg/m^2)	1	21 (1.5)	227	1.00 (reference)	
	2	23 (1.1)	229	0.92	0.75 to 1.13
	3	25 (1.0)	243	0.93	0.76 to 1.14
	4	27 (1.0)	262	0.97	0.80 to 1.19
	5	31 (3.3)	275	1.03	0.85 to 1.26
SBP (mmHg)	1	109 (7.3)	199	1.00 (reference)	
	2	119 (5.5)	221	1.18	0.82 to 1.71
	3	127 (5.1)	249	1.35	0.94 to 1.94
	4	136 (5.3)	259	1.17	0.82 to 1.68
	5	157 (14.8)	305	1.45	1.01 to 2.09
DBP (mmHg)	1	65 (5.5)	176	1.00 (reference)	
	2	73 (4.2)	210	1.22	0.81 to 1.83
	3	79 (3.5)	261	1.37	0.92 to 2.02
	4	84 (4.3)	273	1.66	1.12 to 2.46
	5	95 (8.0)	313	1.84	1.24 to 2.72
Glucose (mmol/l)	1	4.1 (0.52)	257	1.00 (reference)	
	2	4.7 (0.32)	247	0.75	0.41 to 1.36
	3	5.1 (0.32)	236	0.63	0.34 to 1.15
	4	5.5 (0.35)	259	0.79	0.44 to 1.43
	5	6.8 (1.85)	232	0.52	0.28 to 0.96
Cholesterol (mmol/l)	1	4.2 (0.46)	232	1.00 (reference)	
	2	5.0 (0.28)	225	0.83	0.62 to 1.09
	3	5.6 (0.29)	233	0.80	0.61 to 1.06
	4	6.2 (0.34)	266	0.92	0.70 to 1.21
	5	7.4 (0.85)	279	0.90	0.68 to 1.19
Triglycerides (mmol/l)	1	0.7 (0.17)	228	1.00 (reference)	
	2	1.0 (0.21)	231	1.06	0.71 to 1.58
	3	1.3 (0.29)	233	1.00	0.67 to 1.48
	4	1.8 (0.42)	251	1.13	0.76 to 1.68
	5	3.1 (1.54)	259	1.18	0.79 to 1.78

CI, confidence interval; HR, hazard ratio; Q, quintile; RDR, regression dilution ratio; SD, standard deviation.
[a]Follow-up time varied, due to incomplete data, between 6 073 947 (triglycerides) and 6 213 221 person-years (BMI).
[b]Hazard ratio from Cox proportional hazards regression model with attained age as time scale, stratified by cohort, and adjusted for sex, birth year (in decades), baseline age, smoking status, and quintiles of BMI (except in the analysis of BMI itself); HRs are corrected for random error, in which conversion into uncorrected HR = exp((ln(HR))*RDR), with RDR = 0.902 for BMI, RDR = 0.525 for SBP, RDR = 0.497 for DBP, RDR = 0.294 for glucose, RDR = 0.657 for cholesterol, and RDR = 0.465 for triglycerides.

adjustment for the other metabolic factors (hazard ratio = 1.35 per unit, 95% CI 1.05–1.72). High DBP also was related to an increased risk of high-grade glioma (hazard ratio = 1.23 per unit, 95% CI 1.01–1.50). As in the quintile analysis, no relationships were found between *z*-scores of metabolic factors and low-grade glioma.

To further check up the possibility of reverse causation, we re-analysed the blood pressure data after exclusion of the first 5 years of follow-up (data not shown). There was no material differences between these estimates and those presented above, which excluded only the first year of follow-up.

DISCUSSION

In this large pooled cohort study, increased blood pressure was related to the risk of primary brain tumour, particularly of meningioma and high-grade glioma. Risk of meningioma was elevated two to four-fold in three SBP quintiles compared to the lowest quintile. Meningioma risk was also positively related to the combined MetS score, although blood pressure appeared to be the decisive factor in this relationship. Risk of high-grade glioma was particularly related to DBP, with more than doubled risks in the three highest quintiles compared to the lowest quintile. In addition, risk of high-grade glioma was reduced, although not significantly, with higher glucose, suggesting a possible protective effect of high levels of circulating glucose. There is support for a role of energy balance in glioma carcinogenesis [22]. Finally, the risk of high-grade glioma was positively related to triglycerides.

To our knowledge, no previous studies on brain tumours have examined the various MetS factors simultaneously. There are two large cohorts in which brain cancer risks have been studied, the Cancer Prevention Study II cohort with nearly 1900 brain cancer deaths [6,11] and the Swedish Construction Worker Cohort with 918 incident brain cancer cases [12], but the factors investigated were restricted to self-reported diabetes mellitus and BMI; the associations were not significant. Arterial hypertension, in a case–control study of 306 patients with symptomatic meningioma, had a significant odds ratio of 2.23 in the restricted subgroup of 60–69-year-old women, but hypertension was not defined, the analysis did not permit any adjustments for confounders, and the design did not allow any clear conclusions [13]. Three smaller cohort studies, each with many years of follow-up, found no significant associations between blood pressure and brain cancer [14,15,23]. However, these studies suffered from various limitations like limited amount of statistical power, restrictions regarding age, only containing either men or women, incomplete blood pressure measurements, and a large amount of loss to follow-up. In another

TABLE 4. Risk of incident meningioma, low-grade glioma, and high-grade glioma for metabolic factors (quintiles)

		Meningioma[b]			Low-grade glioma			High-grade glioma		
Exposure[a]	Q	*n*	HR[c]	95% CI	*n*	HR[c]	95% CI	*n*	HR[c]	95% CI
BMI (kg/m^2)	1	58	1.00	(reference)	21	1.00	(reference)	65	1.00	(reference)
	2	55	0.87	0.58 to 1.32	16	0.69	0.33 to 1.42	72	0.98	0.68 to 1.43
	3	65	1.01	0.68 to 1.49	21	0.90	0.46 to 1.77	82	1.06	0.73 to 1.52
	4	70	1.05	0.71 to 1.56	24	1.00	0.51 to 1.95	99	1.23	0.87 to 1.75
	5	90	1.39	0.96 to 2.03	16	0.66	0.31 to 1.38	92	1.14	0.80 to 1.64
SBP (mmHg)	1	36	1.00	(reference)	19	1.00	(reference)	62	1.00	(reference)
	2	59	2.58	1.17 to 5.71	13	0.45	0.12 to 1.74	74	1.34	0.70 to 2.55
	3	79	3.60	1.68 to 7.70	17	0.74	0.21 to 2.61	87	1.69	0.90 to 3.18
	4	61	1.93	0.87 to 4.30	25	1.28	0.39 to 4.15	91	1.30	0.69 to 2.44
	5	101	4.26	1.98 to 9.17	24	1.37	0.40 to 4.73	96	1.29	0.68 to 2.46
DBP (mmHg)	1	48	1.00	(reference)	16	1.00	(reference)	47	1.00	(reference)
	2	47	0.75	0.33 to 1.69	16	1.17	0.29 to 4.80	71	1.90	0.90 to 4.01
	3	59	0.95	0.44 to 2.07	21	1.14	0.30 to 4.30	93	2.07	1.01 to 4.23
	4	77	1.47	0.70 to 3.11	25	2.28	0.62 to 8.43	91	2.27	1.10 to 4.70
	5	105	2.33	1.13 to 4.85	20	1.27	0.31 to 5.22	108	2.67	1.29 to 5.50
Glucose (mmol/l)	1	61	1.00	(reference)	14	1.00	(reference)	88	1.00	(reference)
	2	70	1.13	0.35 to 3.66	21	3.93	0.39 to 39.37	78	0.60	0.21 to 1.69
	3	61	0.75	0.22 to 2.53	21	4.22	0.42 to 42.55	84	0.70	0.25 to 1.94
	4	71	1.05	0.32 to 3.38	23	5.85	0.60 to 57.07	81	0.60	0.21 to 1.68
	5	73	1.12	0.35 to 3.62	19	3.28	0.30 to 35.65	77	0.45	0.16 to 1.29
Cholesterol (mmol/l)	1	51	1.00	(reference)	22	1.00	(reference)	73	1.00	(reference)
	2	51	0.92	0.51 to 1.67	17	0.66	0.25 to 1.75	76	0.85	0.52 to 1.38
	3	67	1.27	0.72 to 2.23	16	0.59	0.22 to 1.62	83	0.87	0.54 to 1.42
	4	83	1.63	0.94 to 2.82	21	0.88	0.34 to 2.28	85	0.83	0.51 to 1.35
	5	86	1.52	0.87 to 2.66	22	0.89	0.34 to 2.34	92	0.83	0.51 to 1.36
Triglycerides (mmol/l)	1	58	1.00	(reference)	18	1.00	(reference)	76	1.00	(reference)
	2	66	1.50	0.70 to 3.23	16	0.85	0.20 to 3.64	58	0.53	0.25 to 1.11
	3	69	1.34	0.62 to 2.87	16	0.85	0.19 to 3.67	79	0.94	0.47 to 1.87
	4	63	0.99	0.45 to 2.19	28	2.87	0.77 to 10.72	83	0.99	0.49 to 1.96
	5	72	1.18	0.53 to 2.60	15	0.79	0.17 to 3.75	102	1.48	0.75 to 2.91

CI, confidence interval; HR, hazard ratio; *n*, number of participants; Q quintile.
[a]Follow-up time varied, due to incomplete data, between 4 581 928 (triglycerides) and 4 712 797 person-years (BMI) for meningioma as endpoint, and between 6 073 947 (triglycerides) and 6 213 221 person-years (BMI) for the other endpoints.
[b]Meningioma data in the Norwegian and Swedish cohorts only.
[c]Hazard ratio from Cox proportional hazards regression model: see footnote of Table 3 for details.

cohort study, the Reykjavík Study, 99 brain cancer cases were diagnosed, during up to 27 years of follow-up [10]. DBP on a continuous scale was associated with a risk increase among females, but this result was significant only in an analysis that adjusted for age alone. After adjustment for other risk factors DBP did not have a significant effect, nor were significant associations found for SBP, hypertension, or hypertensive drug use. Again, we believe this study also was limited by the small number of study events. All in all, the current study seems to be the first to investigate both blood pressure and other MetS factors in a cohort study large and valid enough to ascertain relationships with brain tumour occurrence.

For the analysis of blood pressure in quintiles, separate cut-points were used according to sex and cohort, in order to account for differences between men and women and in measurement methods, temporal trends, and so on in the seven cohorts. As a result, the quintile groups had some overlap in absolute levels of blood pressure. As illustration of the distribution of blood pressure values, in the first quintile of SBP the middle 80% of patients had values between 100 and 118 mmHg, compared to between 142 and 178 mmHg in the fifth quintile. The corresponding values for DBP were 59–70 mmHg and 87–105 mmHg, respectively. As noted above, there were strong risk associations such as the four-fold increase in risk of meningioma in the fifth quintile of SBP compared to the reference (see Table 4). In addition, the *z*-score results can also be directly related to blood pressure increase, since 1 standard deviation of SBP is equivalent to 18 mmHg and of DBP to 11 mmHg. Thus, for example, for DBP the risk of high-grade glioma was elevated by 23% per 11 mmHg increase (see Table 5).

Our study had a prospective, population-based cohort design with a large number of participants and is, to the best of our knowledge, the only study to date with enough valid information to investigate the relation between MetS factors and risk of brain tumours. With nearly seven million person-years of follow-up time and more than 1000 brain tumour endpoints, the statistical power was large, enabling us to detect even relatively modest risk effects, to examine associations for each of the major tumour types, and to minimize possible reverse causation by excluding cases diagnosed early after baseline measurement. The follow-up was fairly complete due to high-quality registries for endpoint determination and due to little loss to follow-up of patients. In addition, information on several confounders was available, and repeated measurements of the exposure variables allowed handling of regression dilution bias, leading to better risk estimates.

Our study does, however, have some limitations. We had no information on brain tumour types other than

TABLE 5. Risk of incident brain tumour and subtypes for metabolic factors (*z*-scores)

		All brain tumours		Meningioma[c]		Low-grade glioma		High-grade glioma	
Exposure[a]	m[b]	HR[d]	95% CI	HR[d]	95% CI	HR[d]	95% CI	HR[d]	95% CI
BMI	I	1.03	0.97 to 1.10	1.12	1.00 to 1.26	0.87	0.68 to 1.11	1.09	0.98 to 1.21
	II	0.99	0.91 to 1.08	1.01	0.87 to 1.17	0.79	0.57 to 1.07	1.04	0.90 to 1.20
SBP	I	1.09	0.97 to 1.21	1.41	1.16 to 1.78	1.08	0.72 to 1.61	1.02	0.85 to 1.24
	III	1.08	0.96 to 1.21	1.27	1.03 to 1.57	1.07	0.70 to 1.64	1.03	0.84 to 1.26
DBP	I	1.18	1.05 to 1.32	1.43	1.16 to 1.78	1.03	0.68 to 1.57	1.23	1.01 to 1.50
	III	1.16	1.04 to 1.30	1.29	1.04 to 1.58	0.97	0.64 to 1.48	1.23	1.01 to 1.50
ln(Glucose)	I	0.94	0.77 to 1.16	1.44	1.01 to 2.07	1.30	0.65 to 2.61	0.80	0.55 to 1.15
	II	0.92	0.74 to 1.15	1.35	0.91 to 1.99	1.56	0.76 to 3.18	0.71	0.48 to 1.06
Cholesterol	I	1.01	0.92 to 1.10	1.14	0.97 to 1.35	0.94	0.68 to 1.29	1.01	0.87 to 1.18
	II	0.97	0.87 to 1.07	1.11	0.91 to 1.34	1.03	0.71 to 1.49	0.89	0.75 to 1.07
ln(Triglycerides)	I	1.08	0.97 to 1.21	1.09	0.88 to 1.36	1.02	0.67 to 1.54	1.28	1.05 to 1.55
	II	1.08	0.93 to 1.24	0.87	0.67 to 1.14	1.00	0.60 to 1.67	1.35	1.05 to 1.72
MetS score[e]	I	1.07	0.98 to 1.16	1.31	1.11 to 1.54	1.03	0.75 to 1.42	1.10	0.94 to 1.28

CI, confidence interval; HR, hazard ratio; ln, natural logarithm (base e); m, model; MetS, metabolic syndrome; RDR, regression dilution ratio.
[a]Follow-up time varied, due to incomplete data, between 4 564 553 (MetS score) and 4 712 797 person-years (BMI) for meningioma as endpoint, and between 6 054 079 (MetS score) and 6 213 221 person-years (BMI) for the other endpoints.
[b]Model I adjusted for sex, birth year (in decades), baseline age, and smoking status; model II adjusted like model I and for all the separate *z*-score factors (blood pressure factor is mean of SBP and DBP); model III like model II but without the combined blood pressure factor.
[c]Meningioma data in the Norwegian and Swedish cohorts only.
[d]Hazard ratio from Cox proportional hazards regression model with attained age as time scale, stratified by cohort, and adjusted for the confounders; HRs in model I corrected for random error, in which conversion into uncorrected HR = exp((ln(HR))∗RDR), with RDR = 0.902 for BMI, RDR = 0.525 for SBP, RDR = 0.497 for DBP, RDR = 0.278 for ln(glucose), RDR = 0.657 for cholesterol, RDR = 0.505 for ln(triglycerides), and RDR = 0.688 for MetS score; HRs in models II and III corrected for random error with regression calibration.
[e]The MetS score: standardization of the sum of all the separate *z*-scores (blood pressure factor is mean of SBP and DBP).

meningioma and high and low-grade glioma. In addition, meningioma events had not been registered in one cohort, leading to some distortion in the overall data. On the contrary, meningioma and high-grade glioma did not give the same results, making it questionable whether one can really group them together into one 'all brain tumours' category. Another limitation is the lack of data on further covariates such as comorbidity and use of medication, particularly hypertension drugs. Apart from the potential residual confounding, long-term antihypertensive use reduces blood pressure levels, whereas its effect on risk of brain tumour is unclear. There have been claims of negative, no, and positive associations between various types of such drugs and cancer [24–26]. Furthermore, with individuals who have high blood pressure, one can expect eventually more neurological examinations to be performed, including brain imaging, because of vascular manifestations, which might again result in earlier detection of a possible tumour. Finally, it must be stressed that although we found various associations, causation cannot be claimed; further research is needed.

In conclusion, in this large cohort study we found that increased blood pressure was associated with an increased brain tumour risk, with the relationship strongest for meningioma risk. DBP and triglycerides were related to an elevated risk of high-grade glioma.

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Conflicts of interest

There are no conflicts of interest.

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