

History of allergic disease and epilepsy and risk of glioma and meningioma (INTERPHONE study group, Germany)

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Abstract The aim of the present analysis was to examine the association of a medical history of asthma, hay fever, eczema, or epilepsy with the risk of glioma and meningioma. Data of a German population-based case-control study included 381 meningioma cases, 366 glioma cases, and 1,494 controls. Participants' histories of asthma, hay fever, eczema, and epilepsy and the respective ages at onset were asked during a personal interview. A small inverse association between allergic condition and both glioma (odds ratio: 0.92; 95% CI: 0.70–1.22) and meningioma (odd ratio: 0.87; 95% CI: 0.66–1.14) was found. For glioma, this inverse association was more pronounced in persons reporting to have asthma compared to other allergic conditions. The positive association between epilepsy and particularly glioma suggests that epilepsy is an early

symptom of the disease. As the association was seen also for epilepsies occurring more than a decade before the diagnosis of glioma, this might indicate either an aetiological role of epilepsy, or a relatively long preclinical phase. In conclusion our study confirms previous findings of case control studies but not those from cohort studies. However, possible selection bias in case control studies might not explain the different results in its entirety.

Keywords Allergy · Asthma · Epilepsy · Hay fever · Eczema · Glioma · Meningioma · Brain tumour · Case control study

Introduction

Different medical conditions have been suggested to play a role in the aetiology of primary brain tumours. Allergic diseases, infectious agents or the respective immunologic responses and some hereditary syndromes were reported to be associated with glioma and meningioma [1–5].

Medical history of allergies was found to be inversely associated with the occurrence of glioma but not with the occurrence of meningioma in adults [6, 7]. A meta-analysis of cohort and case-control studies, pooled relative risk estimates for persons with a history of any allergic disease compared to persons not having such a disease reported for glioma an odds ratio of 0.61 (95% confidence interval (CI): 0.55–0.67) and for meningioma an odd ratio of 0.84 (95% CI 0.72–0.98) [6]. A recent comprehensive case-control study including the Nordic and UK part of the Interphone study which was not considered in the meta-analysis confirmed these results [8]. Cohort studies revealed different results. The results of the three cohort studies mentioned by Schwartzbaum et al. [9] are ambiguous, even though the

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authors confirm the conclusion of the meta-analysis [6]. Hagströmer et al. reported in a cohort of 15,666 patients with atopic dermatitis a statistically significant increased risk of brain tumour [10]. Turner et al. did not find any association between asthma and hay fever with the occurrence of brain cancer in a cohort of more than one million men and women and a follow up of 18 years [11]. A biological mechanism is still not known which explain the inverse association between allergic conditions and glioma mostly found in case control studies. Although there are concerns about the impact of bias in the epidemiological studies, all authors of the previous studies concluded that the observed protective effect of the history of atopic condition on glioma risk is unlikely to be due to bias in its entirety [6, 8, 9].

Only few epidemiological studies investigated the association between epilepsy and glioma and meningioma risk, but they consistently showed a positive association. Even though an increased risk for epilepsy was reported many years before the brain tumour was diagnosed, it has been discussed that epileptic seizures are an early symptom of the brain tumour [12–17]. The accumulation of epileptic seizures in particular in young glioma patients with low grade tumours is well established [12–17], but the precise nature of epileptic seizures in patients with brain tumour is unclear [12].

The aim of the present analysis of the German part of the Interphone study (a multinational case–control study on causes of brain tumours) was to analyse the association between medical history of allergy and epilepsy, and the occurrence of glioma and meningioma.

Materials and methods

A population based case–control study (German part of the international Interphone study) was performed in line with the common Interphone study protocol [18]. Meningioma and glioma cases aged 30–59 years (later extended to 69 years) at the date of diagnoses were ascertained over a diagnostic period between October 15, 2000, and October 31, 2003, in defined study areas around the cities of Bielefeld, Heidelberg/Mannheim, and Mainz [19]. The cases were all patients of the neurosurgical clinics of these four cities with histological confirmed diagnoses of primary glioma or meningioma of the brain, as defined in the Interphone core protocol [18].

A total of 891 eligible patients were involved in the study. The response rate for all cases was 83.8% (in meningioma cases: 88.4%; in glioma cases: 79.6%). For the analysis, data from 366 glioma patients and 381 meningioma patients were available. About 2,449 eligible controls frequency matched to the cases by sex, age, and centre were randomly drawn from the population registries in the three regions (residence registration is compulsory in

Germany). A total of 62.7% of them participated in the study ($n = 1,535$). The participation rate differed only marginally between the three different study regions. When patients or controls were deceased or too ill to be interviewed a proxy interview was conducted with a close relative (usually husband or wife). For 40 glioma cases (3.2%), six of glioma controls (0.5%) but only one meningioma case (0.3%), and one control (0.3%) proxy interviews were performed.

At the end of the interview phase an individual post hoc matching was performed to ensure that cases and their matched controls had the same exposure windows. Two controls were matched to each case on sex, year of birth (± 2 years) and study region. The exposure period of controls was censored at the date of diagnosis of the matched case (reference date). For all analyses, data from 747 cases and 1,494 individually matched controls were used.

Computer assisted personal interviews (CAPI) were conducted with cases and controls by trained interviewers. Details on demographic characteristics, smoking, medical histories, and diagnostic procedures (cases) were collected. Questions on the self reported medical history focused on asthma, hay fever, eczema and epilepsy diagnosed by a physician. Age at onset of each disease was asked and, in addition, for eczema the intermittent periods. For asthma and hay fever, no information was available on stop dates or intermittent periods.

Our analyses were based only on allergic conditions or epilepsies diagnosed at least 2 years before tumour diagnosis for cases, or reference date for controls. Thirty-one glioma and six meningioma patients had to be excluded because they have reported epilepsy less than 2 years before tumour diagnosis, whereas no control had to be excluded for this reason.

Nearly all cases were interviewed during their stay in the hospital, otherwise later at home. The controls were mostly interviewed at their home. The interview was not blinded regarding the disease status, but each interviewer interviewed cases as well as controls. After each interview the interviewer filled in a short questionnaire concerning the assessment of the quality of the given answers from the interviewee.

Conditional logistic regression models for frequency-matched datasets were used to estimate the odds ratio (OR) and its respective 95 percent confidence interval (95% CI). The different models for glioma and meningioma were stratified for study area and sex. Age at diagnosis for cases and age at reference date for controls was not used as a variable for stratification to reduce the amount of strata in the analysis. Instead, modelling age as continuous variable allowed better adjustment for residual confounding. Further variables used for adjustment in all analyses were socio-economic status, urban ($\geq 100,000$ inhabitants)

versus rural areas (<100,000 inhabitants), and smoking history (non-smoker, ex-smoker, current smoker). Socio-economic status (SES) was built using information on educational and occupational training, yielding three levels. History of the three allergic diseases was analysed by duration and by age at onset. In addition, the information on the three allergic diseases was combined as “history of any allergy”. As well as for the duration of the allergic conditions, age at onset was also categorized into three levels: duration <10, 10–19, and ≥ 20 years. Additionally, the adjusted odds ratio was analyzed separately for high grade glioma cases only, because the number of low grade glioma cases was too small for a separate analysis.

For glioma, a sensitivity analysis was performed excluding cases and controls who were classified by the interviewers as not remembering details of their medical history well. In total this occurred in eight cases (all glioma) and six controls (four glioma controls; two meningioma controls). A second sensitivity analysis was done excluding all proxy interviews.

Conditional logistic regression models were also used in the analysis of epilepsy (categorized as epilepsy present/not present). In addition two categories of duration of epilepsy were built (epilepsy diagnosed between 2 and 10 years before tumour diagnosis, and epilepsy diagnosed more than 10 years before diagnosis). The statistical analysis was conducted in SAS 9.1.

Results

The distribution of major demographic characteristics of the study population is presented in Table 1. The median age in cases and controls was 53 years for glioma and 55 years for meningioma. Nearly 60% of glioma cases but only 27% of meningioma cases were male. Compared to cases, controls for both diagnoses had a slightly higher socioeconomic status than their corresponding cases.

Results from the analyses of the history of allergies and the occurrence of glioma and meningioma are presented in Table 2. The adjusted odds ratios did not reveal any statistical significant associations between any allergy, asthma, eczema, hay fever and the occurrence of glioma. However, the odds ratios for asthma pointed towards an inverse association. Similar results were seen for persons with only one allergic condition (only asthma, only eczema, or only hay fever) as well as persons with a concomitance of at least two of these conditions when compared with persons not having any allergy (“not mentioned allergic condition”). The small number of exposed cases in all analyses has to be noted.

The results with regard to the association between allergic conditions and meningioma are also presented in

Table 1 Description of the study population; German INTERPHONE Study (Bielefeld, Heidelberg/Mannheim, and Mainz, 2000–2003)

	Glioma		Meningioma	
	Cases <i>n</i> (%)	Controls <i>n</i> (%)	Cases <i>n</i> (%)	Controls <i>n</i> (%)
Total	366 (100)	732 (100)	381 (100)	762 (100)
Age categories (years)				
<40	60 (16.4)	122 (16.7)	39 (10.2)	77 (10.1)
40 up to <50	83 (22.7)	173 (23.6)	78 (20.5)	166 (21.8)
50 up to <60	113 (30.9)	209 (28.6)	133 (34.9)	259 (34.0)
60 and more	110 (30.1)	228 (31.2)	131 (34.3)	260 (34.1)
Sex				
Male	216 (59.0)	432 (59.0)	103 (27.0)	206 (27.0)
Female	150 (41.0)	300 (41.0)	278 (73.0)	556 (73.0)
Study region				
Mainz	87 (23.8)	180 (24.6)	89 (23.4)	189 (24.8)
Heidelberg/ Mannheim	179 (48.9)	349 (47.7)	193 (50.7)	369 (48.4)
Bielefeld	100 (27.3)	203 (27.7)	99 (26.0)	204 (26.8)
Socioeconomic status				
Low	26 (7.1)	35 (4.8)	37 (9.7)	54 (7.1)
Medium	217 (59.3)	433 (59.2)	238 (62.5)	453 (59.5)
High	123 (33.6)	264 (36.1)	106 (27.8)	255 (33.5)
Living surrounding				
Urban	92 (25.1)	164 (22.4)	101 (26.5)	172 (22.6)
Rural	274 (74.9)	568 (77.6)	280 (73.5)	590 (77.4)
Smoking history				
Current smoker	101 (27.6)	221 (30.2)	92 (24.2)	189 (24.8)
Ex smoker	96 (26.2)	210 (28.7)	97 (25.5)	202 (26.5)
Never smoker	169 (46.2)	301 (41.1)	192 (50.4)	371 (48.7)

Table 2. Overall, the pattern was similar to that for glioma. No statistically significant associations were found, but a general tendency towards an inverse association.

The results of the sensitivity analyses for glioma are shown in Fig. 1. Exclusion of persons who were classified as not well remembering their medical history or proxy interviews did not substantially change the results, but most of the sensitivity analyses showed a slight shift towards the null. For meningioma, the corresponding analysis was not done as the number of exclusions was small (only one case).

In Table 3, results for duration of the allergic condition and age at first diagnosis of glioma are presented. Duration of the allergic condition did not show any association with glioma. Any history of allergic conditions with an onset at the age of 20 years and older was inversely associated with glioma (odds ratio: 0.77; 95% CI: 0.55–1.07). Interestingly, for hay fever and eczema a positive association was seen for participants reported to be affected in childhood (<10 years of age) compared to those not reporting to have

Table 2 Odds ratios from multiple conditional logistic regressions for the association of history of allergic disease and glioma; German INTERPHONE study (Bielefeld, Heidelberg/Mannheim, and Mainz, 2000–2003)

	Glioma				Meningioma			
	Controls	Cases	Adjusted ^a		Controls	Cases	Adjusted ^a	
			OR	95% CI			OR	95% CI
History of any allergy ^c								
Not mentioned allergic disease	505	260	1		511	266	1	
Any history	227	106	0.92	0.70–1.22	251	114	0.87	0.66–1.14
Asthma ^{b, d}								
No asthma	686	350	1		704	357	1	
Asthma	46	15	0.65	0.36–1.19	58	23	0.78	0.47–1.28
Eczema								
No eczema	596	304	1		606	314	1	
Eczema	136	62	0.91	0.65–1.27	156	67	0.84	0.61–1.15
Hay fever								
No hay fever	623	314	1		651	325	1	
Hay fever	109	52	0.96	0.67–1.38	111	55	0.98	0.67–1.39
History of any allergy ^c								
Not mentioned allergic disease	505	260	1		511	266	1	
Only asthma	23	6	0.51	0.20–1.27	21	8	0.72	0.31–1.65
Only eczema	91	45	0.99	0.67–1.47	108	47	0.85	0.58–1.24
Only hay fever	59	32	1.07	0.67–1.69	59	30	0.96	0.60–1.54
At least two allergic diseases	54	22	0.81	0.48–1.37	63	28	0.85	0.53–1.36

^a Conditional logistic regression for frequency-matched datasets stratified for centre and sex, and adjusted for socioeconomic status, urban versus rural, smoking history, and age at diagnosis

^b Glioma analysis: one case is missing in the table due to missing values in the corresponding variable

^c Meningioma analysis: two cases are missing due to missing values in the corresponding variable

^d Meningioma analysis: one case is missing due to missing values in the corresponding variable

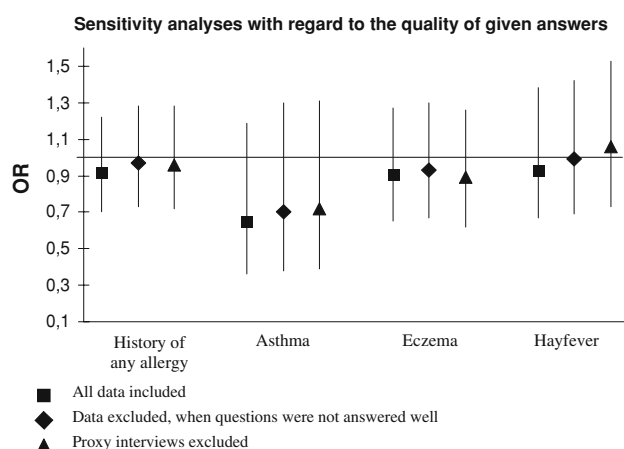


Fig. 1 Sensitivity analyses with regard to the quality of given answers in the history of allergies in glioma patients. German INTERPHONE study (Bielefeld, Heidelberg/Mannheim, and Mainz, 2000–2003)

eczema or hay fever. However, for allergic patients with an age at onset of 20 years and older an inverse association between eczema as well as hay fever and glioma was

found. When restricting the analyses to high grade glioma, risk estimates for allergic conditions were similar to those for all glioma. This was not unexpected, as high grade glioma comprises 79.6% of all glioma cases. All results were not statistically significant.

The association between epilepsy and the occurrence of glioma and meningioma is presented in Table 4. The overall association between epilepsy at least 2 years before the tumour diagnosis and glioma was more pronounced than for meningioma. The analysis of the association between duration of epilepsy and meningioma or glioma risk was based on very small numbers.

Discussion

In the present case control study an inverse but not statistically significant association between self-reported asthma and glioma was observed. These results were concordant to those found in six other case–control studies and one cohort study [8, 9, 13, 20–24]. However, results differed for other types of allergic conditions like hay fever and

Table 3 Odds ratios from multiple conditional logistic regressions for the association of history of allergic disease and glioma; German INTERPHONE study (Bielefeld, Heidelberg/Mannheim, and Mainz, 2000–2003)

	Controls	All glioma cases			High grade glioma cases		
			Adjusted ^a			Adjusted ^a	
		Cases	OR	95% CI	Cases	OR	95% CI
History of any allergy							
No history ^b	505	260	1		207	1	
Duration <10 years	44	16	0.74	0.41–1.34	11	0.64	0.32–1.27
Duration 10–19 years	51	22	0.84	0.50–1.43	16	0.83	0.46–1.50
Duration ≥20 years	128	66	1.03	0.74–1.44	45	0.88	0.60–1.28
No history ^b	505	260	1		207	1	
Age at onset <10 years	20	14	1.49	0.73–3.02	9	1.21	0.54–2.71
Age at onset 10–19 years	40	26	1.30	0.77–2.19	18	1.22	0.68–2.20
Age at onset ≥20 years	165	64	0.77	0.55–1.07	45	0.68	0.47–0.99
Asthma							
No history ^b	686	350	1		269	1	
Duration <10 years	10	2	0.40	0.09–1.84	1	0.25	0.03–2.00
Duration 10–19 years	6	4	1.32	0.37–4.78	1	0.41	0.05–3.52
Duration ≥20 years	28	8	0.59	0.27–1.32	8	0.74	0.33–1.65
No history ^b	686	350	1		269	1	
Age at onset <10 years	15	2	0.29	0.07–1.27	2	0.37	0.08–1.62
Age at onset 10–19 years	4	5	2.42	0.64–9.15	4	2.60	0.64–10.65
Age at onset ≥20 years	25	7	0.56	0.24–1.31	4	0.39	0.13–1.14
Eczema							
No history ^b	596	304	1		236	1	
Duration <10 years	32	11	0.68	0.34–1.37	8	0.67	0.30–1.50
Duration 10–19 years	37	10	0.52	0.26–1.07	7	0.52	0.23–1.18
Duration ≥20 years	65	41	1.26	0.83–1.92	28	1.09	0.68–1.75
No history	596	304	1		236	1	
Age at onset <10 years	12	13	2.21	0.99–4.91	8	1.74	0.70–4.33
Age at onset 10–19 years	29	15	1.63	0.54–1.96	10	0.99	0.47–2.08
Age at onset ≥20 years	95	34	0.71	0.43–1.08	25	0.67	0.42–1.08
Hay fever							
No history ^c	623	314	1		248	1	
Duration <10 years	21	10	0.98	0.45–2.12	3	0.40	0.12–1.36
Duration 10–19 years	31	12	0.77	0.39–1.54	9	0.79	0.37–1.70
Duration ≥20 years	57	29	1.02	0.63–1.63	19	0.86	0.50–1.49
No history ^c	623	314	1		248	1	
Age at onset <10 years	10	8	1.66	0.64–4.28	4	1.13	0.35–3.69
Age at onset 10–19 years	22	10	0.91	0.42–1.96	7	0.87	0.36–2.08
Age at onset ≥20 years	77	33	0.86	0.56–1.33	20	0.68	0.41–1.15

^a Conditional logistic regression for frequency-matched datasets stratified for centre and sex, and adjusted for socioeconomic status, urban versus rural, smoking history, and age at diagnosis

^b Numbers of persons missing is between two and four (not exceeding two cases and/or two controls) due to missing values in the corresponding variable

^c One case is missing due to missing values in the corresponding variable

eczema and study design. One case–control study [22] found no association between hay fever and glioma which is in line with our results whereas two other studies found

an inverse association [8, 23]. For eczema patients, one part of the cohort [9] and three case–control studies [8, 13, 24] found an inverse association with glioma, which was

Table 4 Odds ratios for glioma and meningioma from multiple conditional logistic regressions for the association of history of epilepsy German INTERPHONE study (Bielefeld, Heidelberg/Mannheim, and Mainz), 2000–2003

	Numbers		Adjusted ^a	
	Controls	Cases	OR	95% CI
<i>Glioma</i>				
Epilepsy ^c				
No	709	347	1	
Yes	4	8	4.20	1.25–14.10
Duration of epilepsy ^c				
No epilepsy ^b	709	316	1	
Epilepsy >2 years and ≤10 years before	2	3	3.05	0.50–18.44
Epilepsy >10 years before	2	5	6.23	1.19–32.52
<i>Meningioma</i>				
Epilepsy ^d				
No	729	359	1	
Yes	8	6	1.38	0.47–4.02
Duration of epilepsy ^d				
No epilepsy	729	353	1	
Epilepsy >2 years and ≤10 years before	2	2	2.08	0.29–15.04
Epilepsy >10 years before	6	4	1.17	0.32–4.23

^a Conditional logistic regression for frequency-matched datasets stratified for centre and sex, and adjusted for socioeconomic status, urban versus rural, smoking history, and age at diagnosis

^b Patients with epilepsy 2 years before tumour diagnosis were excluded (31 glioma cases, and 6 meningioma cases and 0 controls)

^c 30 persons are missing due to missing values in the corresponding variable (11 cases and 19 controls)

^d 26 persons are missing due to missing values in the corresponding variable (1 case; 25 controls)

not be observed in our study. Most cohort studies did not find an inverse association between any type of allergic condition and brain tumour [9–11].

The pathophysiological mechanism for the inverse association between allergic condition and glioma and meningioma is still unknown [3, 4]. Genetic or environmental influences on immune reactions may play a role in the association between allergic conditions—in particular in asthma—and brain tumour development. Wiemels et al. reported reduced immunoglobulin E levels in adult glioma patients compared to controls [20]. In a further case–control study Schwartzbaum et al. showed that cases with glioblastoma multiforme compared to controls rarely carry polymorphisms in specific genes—like IL4RA or IL13—that increase the risk for asthma but more often carry specific polymorphisms that decrease the risk for asthma [25]. However, in a replication study with more data the same authors could not confirm these results [26]. The influence of antihistaminic medication against allergies has been investigated in a large study showing also an inverse association with glioma. [13], however, Scheurer et al. reported conflicting results [27]. In summary, recent studies on different polymorphisms and immunoglobulin E serum levels continued to show that further investigations on this topic are necessary to clarify the role of modulation of the

immune system in the protection or promotion of glioma [1, 3–5, 8, 9, 13, 28, 29]. Overall the different result by different study design also reveals ongoing discussion.

In our analysis, eczema or hay fever onset during childhood was found to be weakly positively associated with the occurrence of glioma. With regard to hay fever and eczemas, four case–control studies did not see a trend when age at first diagnosis was taken into account [8, 13, 24, 25]. Therefore, our finding is likely to be due to chance.

Similar results for the inverse association between all allergic conditions and the occurrence of glioma were found for meningioma, which is in line to the results of some other case–control studies even though some of them do not report any association [8, 13, 22, 30]. However, in the meta-analysis of Lino et al. [6] an overall slightly decreased risk for meningioma was seen (odds ratio: 0.84; 95% CI 0.72–0.98).

The strong associations between epilepsy and both glioma and meningioma found in our study were also reported in earlier studies [13, 14, 17]. However, in our questionnaire we specifically asked for diagnosis of epilepsy. It may be expected, that patients report their epileptic seizures as a diagnosis of epilepsy. There was a high number of persons with epileptic seizures, particularly in glioma patients, shortly before the brain tumour

was diagnosed and also the number of persons with epileptic seizures with an onset at least 2 years before the diagnosis of glioma resulting in an increased odds ratio. In meningioma the adjusted odds ratio for epileptic seizures compared to controls was lower which is in line with results from other case–control studies [13, 17, 30]. The occurrence of excess epilepsy several years before brain tumour diagnosis was suggested as a symptom indicating a relatively long preclinical phase of this tumour [17]. In contrast, high grade gliomas are assumed to be fast growing tumours with relatively brief preclinical phases, whereas for low grade gliomas and meningiomas a slower growing is discussed [17]. Due to the small numbers of cases and controls with epileptic seizures, high grade and low grade glioma was not analyzed separately in our study. Although we are in line with previous studies, we cannot exclude that the results are due by chance. The importance of a constant follow-up of patients with epileptic seizure with regard to early diagnosis and better prognosis of the clinical course of brain tumours has been pointed out by different authors [14–16].

The present study has some potential limitations as common in interview-based case–control studies. It is conceivable that short questions, particular on a condition with unspecific symptoms like eczema might be associated with reporting bias. The prevalence of allergic conditions among our controls was 32%, and therewith lower than the 40% reported in a German national health survey conducted in 1999 [31]. This might be due to methodological differences between our study and the health survey such as different age distributions or questionnaires.

As in all retrospective studies, recall bias cannot be excluded. In particular, the condition-related underreporting of allergies in brain tumour cases was discussed in most earlier case–control studies on brain tumours [9, 13, 20, 22, 24, 30] because of possible impairment of cognition or memory [22]. One case–control study also found an effect of underreporting of allergic conditions in proxy interviews of cases [22]. A possible differential underreporting in cases, especially in those who did not answer medical history questions well or in proxy interviews might have lead to a spurious risk reduction, as we have shown in our sensitivity analysis (Fig. 1). As mentioned above, these information biases, particularly with regard to the reduced risk, cannot be excluded.

The potential impact of selection bias in case–control studies also needs to be discussed. The response rates for our study differed between cases (83.8%) and controls (62.7%). Selection bias relating to the exposure of allergic conditions as well as in relation to epilepsy may not be as important as concerning the exposure of cellular phone use, which was the main focus of the Interphone study [19].

The duration of asthma and hay fever was difficult to estimate. Age at onset was asked. However, no information was given whether the allergic condition was still present and, if not, when the symptoms disappeared. Therefore, the duration was only crudely estimated using corresponding age at first diagnosis of the brain tumours and age at onset of these conditions, which might affect the results. Thus, in some persons the duration of asthma and hay fever might be overestimated. Therefore, it is also possible that stronger risk reductions would have been found if we were able to distinguish ongoing allergies from past allergies as it has been done by Wigertz et al. [8]. It should also be noted that this result is hampered by small subgroup analysis and post-hoc classification of those categories.

In conclusion, the present case control study confirms the inverse association between allergic conditions and glioma and meningioma in adults, particularly for asthma and glioma. However, the results were not statistically significant and possible selection bias which might occur in case control studies cannot be excluded. The occurrence of excess epileptic seizure years before brain tumour diagnosis might suggest a relatively long preclinical phase in glioma and might be interpreted as an early symptom.

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