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Association of allergic diseases and epilepsy with risk of glioma, meningioma and acoustic neuroma: results from the INTERPHONE international case-control study

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Abstract:	We investigated the association of allergic diseases and epilepsy with risk of brain tumours, in Interphone, a 13-country case-control study. Data were obtained from 2693 glioma cases, 2396 meningioma cases, and 1102 acoustic neuroma cases and their 6321 controls. Conditional logistic regression models were used to estimate pooled odds ratios (ORs) and their respective 95% confidence intervals (CIs), adjusted for education and time at interview. Reduced ORs were observed for glioma in relation to physician-diagnosed asthma (OR=0.73; CI 0.58-0.92), hay fever (OR 0.72; CI 0.61-0.86), and eczema (OR 0.78, CI 0.64-0.94), but not for meningioma or acoustic neuroma. Previous diagnosis of epilepsy was associated with an increased OR for glioma (2.94; CI 1.87-4.63) and for meningioma (2.12; CI 1.27-3.56), but not for acoustic neuroma. This large-scale case-control study adds to the growing evidence that people with allergies have a lower risk of developing glioma, but not meningioma or acoustic neuroma. It also supports clinical observations of epilepsy prior to the diagnosis of glioma and meningioma.
Response to Reviewers:	Dear Editor, we are very grateful for the helpful comments of the reviewer. Please find our answer below. COMMENTS TO THE AUTHOR: Reviewer #1: EJEP-D-21-01240 The authors present a very well written manuscript. With the amount of sites and coauthors, one can only imagine the coordination work that was necessary before submission. Reviewer: MAJOR POINT Selection Bias The prevalence of allergic diseases, medical diagnosis, and self-report of allergic diseases by individuals is social class-dependent in many nations of Europe. The low response in the control group (44%) was associated with oversampling of the higher social class. Thus, the control group overestimates the exposure prevalence of interest (allergic diseases). This bias may at least partly explain the odds ratio of < 1 for allergic diseases. The authors address this selection bias by statistically adjusting their analyses for education. Please explain how the authors removed the selection bias from the data. I would rather have expected a bias analysis (at least deterministic, preferably probabilistic) for the selection bias. Our answer: We like to thank the reviewer for raising this very important point. Indeed, we observed differences in the response rates by educational level, minor in cases and more so in controls. We observed however only weak associations between prevalence of different allergies and educational level. Taking these two together, we believe there is no major impact by selection bias. We have investigated this in different separate analyses. As already reported, adjustment for educational level did not change any results. Stratified analyses by educational level did not change the results for glioma. For meningioma the risk differed slightly between educational levels, however was still close to 1.00 for any educational level. However, any decreased odds ratio may be explained to a small extent by selection bias.

	We have described this in the discussion (page 18). Reviewer: MINOR POINTS The authors first state that they have performed frequency matching. Then on page 14 they state "Only diagnoses that occurred up to two years prior to the tumor diagnosis (cases) or reference date (controls; date of diagnosis of corresponding case)". Here it sounds like an individual matching was performed. I do not understand this correctly. Our answer: We thank the reviewer for this comment as this was confusing. To make a long story short, controls were drawn in a frequency-matched way but post-hoc individually assigned to cases. This was necessary for the mobile phone-related approach as prevalence changed rapidly over time, and we kept the approach for all other Interphone related analyses. We added this explanation in the Methods. Our procedure for matching is described in more detail in the cited Interphone Paper (Ref 6). Briefly: All 16 study centres selected there controls randomly from the source population. Our study-design called for controls to be individually- or frequency-matched to cases, with 1:1 matching for glioma and meningioma (except Germany which has done 1:2) and 1:2 for acoustic neuroma. Controls were matched on year of birth (within 5-year categories), sex and study region. Canada-Ottawa, Vancouver, France, Israel, Japan, new-Zealand and UK-North matched individually, the other countries used first frequency matching and conducted individual matching post-hoc. Post-hoc matched controls were only those who were interviewed as close as possible in time to the respected case interview (about 3 month) (reference date), in addition to the general matching criteria. For the analyses we stratified for age, sex and study region for different reasons depended on the topic. Therefore we used conditional logistic regression analyses for individual and post-hoc matching. Reviewer: The table layout of tables 1-2 is not comfortable (slashes between numbers of people, etc.). Our answer: We improved the layout of the tables. We left the slashes between cases and controls as we felt this helps for clarity, but removed them otherwise. Also we removed abbreviations and checked for consistency. With best regards, sincerely, on behalf of all authors Brigitte Schlehofer, Maria Blettner, Joachim Schüz

Short Communication

Association of allergic diseases and epilepsy with risk of glioma, meningioma and acoustic neuroma: results from the INTERPHONE international case-control study

Short title: Association of allergic diseases and epilepsy with brain tumours

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Abbreviations

IARC/WHO	International Agency for Research on Cancer / World Health Organisation
ICD-O	International Classification of Diseases for Oncology

CI	95% confidence interval
OR	Odds ratio

Declarations

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Conflicts of interest

The authors confirm that they have no conflicts of interest.

Availability of data

Original data are not available as per ethical clearance and national data privacy legislations.

Code availability

Programming code of analysis used for the present paper can be obtained by contacting the corresponding author.

Authors' contributions

BS, MB and JS designed and jointly led the present project and drafted the manuscript. MM carried out the analysis. All other authors were also involved in the INTERPHONE study, its design, conduct and interpretation. EC was the overall coordinator of the INTERPHONE project. All authors reviewed and approved the manuscript.

Ethics approval

IARC Ethical approval was granted on 25 November 1999 (No ERC-Project 99-010). All study centers obtained national ethical approval.

Consent to participate

All participants of the INTERPHONE study filled in written informed consent.

Consent to publication

All authors critically reviewed and approved the final version of the manuscript.

Disclaimer

Where authors are identified as personnel of IARC/WHO, the authors alone are responsible for the views expressed in this article, and they do not necessarily represent the decisions, policy, or views of IARC/WHO.

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Abstract

We investigated the association of allergic diseases and epilepsy with risk of brain tumours, in Interphone, a 13-country case-control study. Data were obtained from 2693 glioma cases, 2396 meningioma cases, and 1102 acoustic neuroma cases and their 6321 controls. Conditional logistic regression models were used to estimate pooled odds ratios (ORs) and their respective 95% confidence intervals (CIs), adjusted for education and time at interview. Reduced ORs were observed for glioma in relation to physician-diagnosed asthma (OR=0.73; CI 0.58-0.92), hay fever (OR 0.72; CI 0.61-0.86), and eczema (OR 0.78, CI 0.64-0.94), but not for meningioma or acoustic neuroma. Previous diagnosis of epilepsy was associated with an increased OR for glioma (2.94; CI 1.87-4.63) and for meningioma (2.12; CI 1.27-3.56), but not for acoustic neuroma. This large-scale case-control study adds to the growing evidence that people with allergies have a lower risk of developing glioma, but not meningioma or acoustic neuroma. It also supports clinical observations of epilepsy prior to the diagnosis of glioma and meningioma.

Key words: allergies, epilepsy, brain tumours, multicenter case-control study

Introduction

Epidemiological studies have consistently found an inverse association between a history of allergic diseases and risk of glioma, while results were conflicting for meningioma and acoustic neuroma [1-3]**.** Underlying biological mechanisms appear to be complex; however, there is agreement that immunologic functions play an important role in the development of brain tumours, and allergic diseases probably indicate an effective immunosurveillance system [1, 2]. Epilepsy or epileptic seizures can occur as early symptoms of brain tumors and it has been hypothesized that seizure susceptibility increases due to interaction between tumor cell metabolism and the neuronal network [4, 5].

Interphone is an international multi-center case-control study carried out in 13 countries and coordinated by IARC/WHO [6]. It focused on the association between mobile phone use and brain tumours, but data on allergic diseases and epilepsy were also collected. Here we report the results from the analysis of the pooled data set from the sixteen study centers on the associations between history of allergic diseases and epilepsy and risk of glioma, meningioma and acoustic neuroma.

Methods

The study population consists of incident, histologically or imaging-confirmed cases of glioma, meningioma and acoustic neuroma occurring between 2000 and 2004, 30-59 years old at diagnosis and their controls (sampled in frequency-matched manner and post-hoc individually

assigned with one per case for glioma and meningioma, two per case for acoustic neuroma). Controls were matched on age, sex, and study region (for details see [6, 7]).

Interviews were performed by trained interviewers, mainly using a computer-assisted questionnaire, either face-to-face (93.9 % cases, 99.5 % controls) or by telephone. Proxy interviews were conducted when the participant was too ill or deceased. This was the case for 336 glioma cases, 41 meningioma cases, 3 acoustic neuroma cases and 40 controls. The interview captured information on mobile phone use, ionizing and non-ionizing medical radiation exposures, socio-demographic factors and other potential risk factors for brain tumours. In addition, a history of various physician-diagnosed medical conditions, were asked, including diagnoses of asthma, hay fever, and eczema; which are conditions thought to reflect allergic reactions. Details were asked about the age at onset of these diseases, and for eczema the age when the symptoms stopped. Similar questions were asked for epilepsy.

Statistical approaches followed the strategy of all analyses of the Interphone study (for details see [6-7]). Conditional logistic regression models were used to estimate pooled odds ratios (ORs) and their 95% confidence intervals (CIs), adjusted for education and time interval between case and respective control interviews. Analyses were performed for each brain tumour type, and for men and women separately, or - if analysis was performed for men and women combined - adjusted for gender. Subgroup analyses were done separately for high-grade (type III-IV) and low-grade (type I and II) glioma, based on ICD-O morphological codes (details see [6, 7]).

Reference categories were defined as “never diagnosed with allergy” and ”never diagnosed with epilepsy”, respectively, as reported by the study subjects. Only diagnoses that occurred up to two years prior to the tumour diagnosis (cases) or reference date (controls; date of diagnosis of corresponding case) were included. Missing data was less than 5% for epilepsy and less than 1% for the allergies.

For each asthma, hay fever, and eczema, we created a binary variable (ever/never). We also investigated whether time since first diagnosis (< 10 years, 10 - 19 years, ≥20 years) or age at onset (< 10 years, 10 – 19 years, ≥20 years) was associated with the diseases. For eczema, we distinguished past and current rash. We also estimated ORs for one or more than one allergy compared with no allergy. Sensitivity analyses were performed by excluding proxy interviews and by including smoking as a potential confounder, but made no difference to the main results (data not shown).

Results

In total, the analyses included data from 2693 glioma cases (62.6% response rate), 2396 meningioma cases (76.9%) and 1102 acoustic neuroma cases (81.0%) and 6321 control subjects (44%). The distribution of cases and controls by selected demographic factors is presented in Supplementary Table 1. For all tumour types, educational level was slightly higher for controls than for cases.

For glioma, ORs below 1 were found for participants who were ever diagnosed with asthma (OR 0.73, CI 0.58-0.92), hay fever (OR 0.72, CI 0.61-0.86) or eczema (OR 0.78, CI 0.64-0.94), or "any allergy" (OR 0.71, CI 0.61-0.82) (Table 1). The result for eczema was driven by those with current rash. ORs were lowest when the allergies occurred less than ten years before glioma tumour diagnosis, and for those whose allergies started in adulthood. Subdivision into high grade and low grade glioma showed that the decrease was driven by the results for high-grade glioma (Table 1). For meningioma, no association was seen in relation to asthma (OR 0.91, CI 0.72-1.14) or to hay fever (OR 0.91, CI 0.76-1.10), but eczema showed a slightly lower risk (OR 0.84, CI 0.70-1.02), that was more pronounced for those with current rash (OR 0.76; CI 0.60-0.95) (Table 1). For both tumour types there was little difference in ORs between men and women, but for hay fever and eczema the ORs for men were somewhat lower (Table 2).

For acoustic neuroma no association was found with asthma (OR 1.02, CI 0.75-1.37), hay fever (OR 0.91, CI 0.72-1.14), or eczema (OR 1.02, CI 0.78-1.32), overall and by time since start of the allergy or by age at onset. The results were similar for men and women (Tables 1 and 2).

A prior diagnosis of epilepsy was associated with an increased OR for glioma (OR 2.94, CI 1.87-4.63) and for meningioma (OR 2.12, CI 1.27-3.56) (Table1). Subgroup analyses for glioma and meningioma and epilepsy were based on small numbers (Tables 1 and 2). However, for both glioma and meningioma, sex-specific analyses revealed higher risks for men than for women. The OR was higher for low-grade glioma (OR 5.71, CI 2.48-13.1) compared with high-grade glioma (OR 2.01, CI 1.14-3.54). For both glioma and meningioma, the highest ORs were seen for adult-onset epilepsy, and for subjects whose epilepsy was diagnosed less than 10 years before

the reference date. ORs were not increased for acoustic neuroma (Table 1), however, analyses were based on small numbers of subjects with epilepsy.

Discussion

These results presented were based on data from all Interphone study centres [6, 7]. Some differences in results published from single or smaller groups of study centres [e.g. 3, as most recent], may be due to chance or to differences in participation rates, prevalence of specific diseases or other factors.

Allergic diseases

We found inverse associations of asthma, hay fever and eczema with risk of glioma, especially for high-grade glioma, for both men and women. Allergic diseases diagnosed closer to the diagnosis of the high-grade glioma (less than 10 years) were associated with lower ORs than those diagnosed earlier and at early ages. Our findings are consistent with previous studies, a recent meta-analysis [8] and review [9]. Overall, no association was seen between low-grade glioma, meningioma, and acoustic neuroma with any of the three allergic diseases [1]. Decreased ORs were observed, however, for low grade glioma and for meningioma for those who at time of interview reported current eczema.

Prospective studies found lower levels of total or respiratory-specific immunoglobulin IgE, a biomarker of allergy, in glioma patients, strengthening our observation of an inverse

association [1, 8]. The underlying biogenetic mechanism is not fully understood. The immediate hypersensitivity reactions of these three allergies are mediated by IgE, and this may be influenced by preclinical tumours. Further investigations of immunologic mechanisms, for example in the immunosurveillance system, and investigations of germline SNPs or genetic risk factors are needed for better understanding of the mechanism [2].

History of Epilepsy

In line with earlier epidemiological studies and clinical observations, we found elevated ORs of glioma and meningioma in relation to past epilepsy with the highest ORs for low-grade glioma, a finding also described by other studies [4]. No association was seen between history of epilepsy and acoustic neuroma but numbers of subjects were small. Epilepsy and epileptic seizures prior, but close to the diagnosis of glioma or meningioma are known to be important symptoms of brain tumours as an early warning sign and a prognostic factor for survival [5]. Different hypotheses concerning the epileptogenesis in tumour cells and peritumoral cells have been discussed, e.g. that an aberrant tumour cell metabolism may influence the neuronal network leading to seizures [4, 10].

Strengths and Limitations

This is to our knowledge the largest ever case-control study on this topic. With all centres following the same study protocol, no compromises had to be made when pooling the data. Participation proportions in cases (glioma 63%, meningioma 77% and acoustic neuroma 81%) were high and the distribution of cases by sex and age was as to be expected for the respective

tumours types. For glioma, proxy interviews were used for 12% of cases, but excluding them had little effect on the results. Main limitations were the low response proportion among controls and the fact that all data on medical diagnoses were based on self-reports of a physician diagnosis, leading to concerns about potential selection and recall bias.

Selection bias was of particular concern as response rates did somewhat differ by education (lower with shorter education) and prevalence of allergies may also differ by education; but in fact the association between allergies and education was weak (data not shown). Odds ratios with or without adjustment for education did hardly differ. Stratified analysis by education did not show any differences for glioma. For meningioma, the odds ratios differed slightly between groups, but were close to 1 for any educational level. Hence we conclude that the inverse association for glioma is not due to selection bias but the minor decrease in odds ratios for meningioma may well be.

Conclusions

Findings from this large-scale, international case-control study with a representative distribution of cases for the respective tumour types, add to the growing evidence that people with allergies have a lower risk of glioma than those without allergies, especially for high-grade glioma, but not for meningioma or acoustic neuroma. It also confirms the association between epilepsy and glioma and meningioma, most likely due to epilepsy being a symptom for a sizeable proportion of these tumours.

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Table 1: Association between tumour and allergy or epilepsy, by time since start[1] and age at onset[2]

	Glioma		low grade glioma		high grade glioma		meningioma		acoustic neuroma	
	cases/ controls	OR (95% CI)	cases/ controls	OR (95% CI)	cases/ controls	OR (95% CI-)	cases/ controls	OR (95% CI)	cases/ controls	OR (95% CI)
Asthma										
Ever/never										
never	2453/2630	1.00	751/797	1.00	1678/1805	1.00	2161/2377	1.00	1001/1928	1.00
ever	220/303	0.73 (0.58-0.92)	82/107	0.89 (0.60-1.34)	137/196	0.65 (0.49-0.87)	228/263	0.91 (0.72-1.14)	99/204	1.02 (0.75-1.37)
Time since start										
never	2453/2630	1.00	751/797	1.00	1678/1805	1.00	2161/2377	1.00	1001/1928	1.00
< 10 years	49/92	0.67 (0.44-1.02)	25/29	1.05 (0.53-2.08)	23/63	0.47 (0.26-0.85)	66/73	0.91 (0.62-1.34)	34/70	0.99 (0.59-1.64)
10-19 years	37/60	0.53 (0.32-0.88)	18/25	0.80 (0.37-1.74)	19/35	0.36 (0.17-0.76)	54/51	1.18 (0.71-1.94)	13/32	0.62 (0.28-1.37)
20 + years	134/151	0.85 (0.63-1.15)	39/53	0.84 (0.48-1.49)	95/98	0.84 (0.59-1.21)	108/139	0.83 (0.61-1.13)	52/102	1.20 (0.80-1.80)
Age at onset										
never	2453/2630	1.00	751/797	1.00	1678/1805	1.00	2161/2377	1.00	1001/1928	1.00
child (0-9)	93/103	0.80 (0.56-1.15)	22/38	0.66 (0.33-1.30)	71/65	0.87 (0.57-1.33)	53/82	0.57 (0.36-0.89)	36/61	1.30 (0.79-2.15)
young (10-19)	39/43	0.95 (0.55-1.64)	17/20	0.83 (0.36-1.92)	22/23	1.09 (0.54-2.23)	39/33	1.37 (0.79-2.40)	15/30	1.29 (0.60-2.78)
adult (20+)	88/157	0.62 (0.45-0.86)	43/49	1.09 (0.64-1.86)	44/108	0.40 (0.26-0.63)	136/148	1.00 (0.75-1.33)	48/113	0.81 (0.54-1.23)
Hay Fever										
Ever/never										
never	2251/2365	1.00	684/713	1.00	1546/1628	1.00	2006/2162	1.00	895/1720	1.00
ever	410/558	0.72 (0.61-0.86)	150/194	0.86 (0.63-1.15)	256/360	0.67 (0.54-0.84)	370/465	0.91 (0.76-1.10)	201/402	0.91 (0.72-1.14)
Time since start										
never	2251/2365	1.00	684/713	1.00	1546/1628	1.00	2006/2162	1.00	895/1720	1.00
< 10 years	80/117	0.67 (0.47-0.96)	30/41	0.99 (0.57-1.73)	49/76	0.53 (0.33-0.85)	82/105	0.96 (0.66-1.40)	54/99	0.95 (0.61-1.48)
10 – 19 years	75/126	0.56 (0.39-0.79)	28/48	0.52 (0.27-0.99)	46/76	0.57 (0.36-0.89)	83/109	0.86 (0.61-1.21)	41/92	0.77 (0.49-1.22)
20 + years	255/315	0.81 (0.66-1.01)	92/105	0.95 (0.65-1.38)	161/208	0.77 (0.59-1.01)	205/251	0.92 (0.73-1.16)	106/211	0.95 (0.71-1.28)
Age at onset (years)										
Never	2251/2365	1.00	684/713	1.00	1546/1628	1.00	2006/2162	1.00	895/1720	1.00
0-9	89/107	0.84 (0.59-1.21)	34/39	0.99 (0.55-1.78)	55/67	0.77 (0.48-1.24)	58/68	1.04 (0.68-1.58)	32/64	0.96 (0.58-1.59)

10-19	131/174 0.75 (0.56-1.00)	51/69 0.80 (0.50-1.28)	79/103 0.77 (0.53-1.12)	106/128 0.85 (0.63-1.16)	59/122 0.95 (0.64-1.39)
20+	190/277 0.67 (0.53-0.84)	65/86 0.84 (0.55-1.28)	122/190 0.60 (0.45-0.80)	206/269 0.92 (0.72-1.16)	110/216 0.87 (0.64-1.18)
Eczema					
Ever/never					
never	2350/2491 1.00	723/762 1.00	1605/1707 1.00	2064/2207 1.00	954/1791 1.00
ever	313/435 0.78 (0.64-0.94)	110/145 0.73 (0.51-1.03)	200/284 0.78 (0.61-0.98)	316/426 0.84 (0.70-1.02)	145/333 1.02 (0.78-1.32)
Time since start (years)					
never	2350/2491 1.00	723/762 1.00	1605/1707 1.00	2064/2207 1.00	954/1791 1.00
< 10	55/108 0.58 (0.39-0.85)	21/41 0.48 (0.25-0.92)	34/65 0.66 (0.40-1.08)	58/97 0.81 (0.55-1.21)	26/81 0.79 (0.46-1.37)
10 -19	69/83 0.91 (0.62-1.34)	24/23 0.79 (0.37-1.67)	43/59 0.87 (0.54-1.40)	66/73 1.03 (0.68-1.55)	32/70 1.09 (0.64-1.87)
20 +	189/244 0.82 (0.65-1.05)	65/81 0.85 (0.56-1.31)	123/160 0.79 (0.59-1.07)	192/256 0.81 (0.64-1.02)	87/182 1.09 (0.79-1.51)
Age at onset (years)					
Never	2350/2491 1.00	723/762 1.00	1605/1707 1.00	2064/2207 1.00	954/1791 1.00
0-9	93/125 0.75 (0.53-1.05)	35/51 0.75 (0.44-1.27)	57/70 0.76 (0.48-1.21)	89/108 0.81 (0.59-1.13)	44/92 0.93 (0.60-1.44)
10-19	77/87 1.07 (0.74-1.54)	29/25 1.10 (0.55-2.19)	47/62 0.98 (0.63-1.55)	67/97 0.83 (0.57-1.21)	33/65 1.36 (0.80-2.31)
20+	143/223 0.68 (0.53-0.89)	46/69 0.57 (0.34-0.94)	96/152 0.70 (0.51-0.97)	160/221 0.87 (0.67-1.12)	68/176 0.96 (0.67-1.37)
Past/current					
Never	2348/2485 1.00	722/761 1.00	1604/1702 1.00	2060/2200 1.00	954/1784 1.00
Past	127/138 1.01 (0.74-1.37)	47/44 1.01 (0.58-1.77)	79/93 0.95 (0.65-1.39)	125/135 1.03 (0.75-1.40)	55/107 1.13 (0.73-1.74)
Current	179/291 0.67 (0.53-0.85)	61/98 0.63 (0.42-0.95)	116/188 0.68 (0.51-0.91)	184/283 0.76 (0.60-0.95)	87/218 0.96 (0.71-1.32)
Allergies					
Any allergy					
None	1903/1894 1.00	568/565 1.00	1316/1309 1.00	1661/1731 1.00	757/1393 1.00
at least one	721/989 0.71 (0.61-0.82)	253/327 0.78 (0.60-1.01)	462/654 0.67 (0.56-0.80)	699/878 0.86 (0.74-1.00)	336/715 0.91 (0.75-1.11)
Time since start (years)					
Never	1903/1894 1.00	568/565 1.00	1316/1309 1.00	1661/1731 1.00	757/1393 1.00
< 10	126/229 0.56 (0.42-0.74)	47/74 0.68 (0.42-1.09)	78/154 0.50 (0.35-0.71)	135/189 0.77 (0.58-1.03)	81/178 0.85 (0.59-1.21)
10 – 19	137/196 0.65 (0.49-0.86)	51/68 0.63 (0.38-1.03)	83/126 0.61 (0.43-0.87)	144/177 0.84 (0.63-1.12)	65/145 0.81 (0.55-1.17)
20 +	458/564 0.79 (0.66-0.94)	155/185 0.88 (0.65-1.20)	301/374 0.75 (0.61-0.93)	420/512 0.89 (0.75-1.06)	190/392 0.98 (0.77-1.24)
Age at onset (years)					

Never	1903/1894	1.00	568/565	1.00	1316/1309	1.00	1661/1731	1.00	757/1393	1.00
0-9	215/281	0.71 (0.56-0.90)	72/104	0.77 (0.52-1.15)	142/172	0.69 (0.51-0.94)	171/209	0.83 (0.64-1.07)	87/177	0.95 (0.68-1.32)
10-19	193/233	0.84 (0.65-1.07)	76/82	0.89 (0.57-1.38)	115/150	0.80 (0.59-1.10)	169/202	0.93 (0.72-1.20)	82/167	1.06 (0.75-1.49)
20+	313/475	0.65 (0.53-0.78)	105/141	0.73 (0.51-1.04)	205/332	0.60 (0.47-0.76)	359/467	0.84 (0.70-1.02)	167/371	0.83 (0.64-1.07)
Epilepsy										
Ever/never										
Never	2499/2811	1.00	775/882	1.00	1701/1902	1.00	2276/2532	1.00	1061/2057	1.00
Ever	101/33	2.94 (1.87-4.63)	48/10	5.71 (2.48-13.1)	52/23	2.01 (1.14-3.54)	61/32	2.12 (1.27-3.56)	17/26	1.44 (0.68-3.07)
Time since start (years)										
Never	2499/2811	1.00	775/882	1.00	1701/1902	1.00	2276/2532	1.00	1061/2057	1.00
< 10	52/7	8.44 (3.28-21.7)	25/2	21.7 (2.89-163)	26/5	5.09 (1.66-15.6)	21/5	6.73 (1.90-23.9)	1/8	0.16 (0.01-1.84)
10 – 19	21/4	3.62 (1.09-12.0)	14/3	3.64 (0.91-14.5)	7/1	3.38 (0.38-30.4)	12/2	4.37 (0.83-22.9)	5/2	15.7 (1.00-242)
20 +	28/22	1.28 (0.67-2.46)	9/5	2.15 (0.50-9.23)	19/17	1.09 (0.51-2.32)	28/25	1.32 (0.71-2.43)	11/16	1.70 (0.68-4.28)
Age at onset (years)										
Never	2499/2811	1.00	775/882	1.00	1701/1902	1.00	2276/2532	1.00	1061/2057	1.00
0-9	9/10	0.97 (0.31-2.99)	5/3	3.52 (0.33-37.8)	4/7	0.63 (0.16-2.45)	14/13	1.24 (0.51-3.02)	3/5	1.38 (0.32-6.02)
10-19	15/11	0.94 (0.38-2.33)	7/3	1.72 (0.39-7.57)	8/8	0.61 (0.18-2.02)	10/5	1.52 (0.45-5.10)	6/8	2.66 (0.72-9.76)
20+	77/12	6.61 (3.30-13.2)	36/4	10.68 (3.15-36)	40/8	4.89 (2.07-11.6)	37/14	3.35 (1.58-7.10)	8/13	0.90 (0.27-2.98)

[1]Between first diagnosis by a physician and two years before tumour diagnosis (cases) or reference date (controls)

[2]Reference category (never): no diagnosis of disease up to two years before tumour diagnosis (cases) or reference date (controls); adjusted for education and time at interview; cases and controls answering "don't know" for a disease or having missing values in the adjustment variables were excluded from analyses

Table 2: Association between tumour and allergy or epilepsy, by gender[1]

	glioma - men		glioma - women		meningioma - men		meningioma - women		acoustic neuroma – men		acoustic neuroma – women	
	cases/ controls	OR (95% CI)	cases/ controls	OR (95% CI)	cases/ controls	OR (95% CI)	cases/ controls	OR (95% CI)	cases/ controls	OR (95% CI)	cases/ controls	OR (95% CI)
Asthma												
never	1477/1590	1.00	976/1040	1.00	519/575	1.00	1642/1802	1.00	488/943	1.00	513/985	1.00
ever	127/165	0.75 (0.55-1.02)	93/138	0.71 (0.50-1.02)	45/52	1.00 (0.61-1.63)	183/211	0.88 (0.68-1.14)	47/87	1.02 (0.63-1.63)	52/117	0.95 (0.64-1.42)
Hay Fever												
never	1360/1428	1.00	891/937	1.00	483/533	1.00	1523/1629	1.00	440/843	1.00	455/877	1.00
ever	234/319	0.67 (0.53-0.85)	176/239	0.75 (0.58-0.98)	81/95	0.87 (0.58-1.31)	289/370	0.91 (0.74-1.12)	93/181	0.93 (0.65-1.32)	108/221	0.85 (0.62-1.16)
Eczema												
never	1446/1536	1.00	904/955	1.00	521/552	1.00	1543/1655	1.00	473/898	1.00	481/893	1.00
ever	150/214	0.74 (0.56-0.97)	163/221	0.80 (0.61-1.05)	44/78	0.59 (0.36-0.94)	272/348	0.91 (0.74-1.12)	62/129	1.01 (0.65-1.55)	83/204	1.04 (0.74-1.45)
Any allergy												
none	1174/1176	1.00	729/718	1.00	423/445	1.00	1238/1286	1.00	378/708	1.00	379/685	1.00
1 and more	400/549	0.66 (0.54-0.80)	321/440	0.75 (0.6-0.94)	137/177	0.77 (0.56-1.06)	562/701	0.88 (0.74-1.04)	153/309	0.93 (0.69-1.27)	183/406	0.87 (0.67-1.14)
Epilepsy												
never	1493/1675	1.00	1006/1136	1.00	530/603	1.00	1746/1929	1.00	514/989	1.00	547/1068	1.00
ever	62/20	3.71 (2.02-6.82)	39/13	2.37 (1.16-4.81)	20/5	5.46 (1.67-17.8)	41/27	1.55 (0.86-2.79)	8/11	2.23 (0.65-7.66)	9/15	1.26 (0.46-3.43)

[1]Reference category (never): no symptoms of disease up to two years before tumour diagnosis (cases) or reference date (controls); adjusted for education and time at interview; cases and controls answering "don't know" for a disease or had missing values in the adjustment variables were excluded from analyses

Supplementary table: Description of the study population for the analyses of allergic conditions and epilepsy. Interphone Study Group

	Glioma Cases		**meningioma cases**		**acoustic neuroma cases**		**controls[1]**	
	n	%	n	%	n	%	n	%
Status of interview								
total ascertained	4301	100	3115	100	1361	100	14354	100
not interviewed	1536	36	690	22	240	18	6696	47
Interviewed	2765	64	2425	78	1121	82	7658	53
Reasons for exclusion								
not interviewed	1536	*100*	690	*100*	240	*100*	6696	*100*
Refused	*470*	*31*	*339*	*49*	*148*	*62*	*4303*	*64*
doctor refusal	*198*	*13*	*69*	*10*	*23*	*10*	*126*	*2*
dead or too ill	*637*	*42*	*66*	*10*	*5*	*2*	*49*	*1*
language problems	*34*	*2*	*50*	*7*	*12*	*5*	*133*	*2*
unable to trace	*157*	*10*	*137*	*20*	*46*	*19*	*1819*	*27*
other reasons	*40*	*3*	*29*	*4*	*6*	*3*	*266*	*4*
Interviewed but excluded[2]	72		29		19		1337	

	Glioma				**meningioma**				**acoustic neuroma**			
	cases		**controls**		**cases**		**controls**		**cases**		**Controls**	
	n	*%*	**n**	*%*	**n**	*%*	**n**	*%*	**n**	*%*	**n**	*%*
inclusion in analyses	**2693**	*100*	**2957**	*100*	**2396**	*100*	**2649**	*100*	**1102**	*100*	**2137**	*100*
Men	1614	*60*	1768	*60*	569	*24*	634	*24*	536	*49*	1032	*48*
women	1079	*40*	1189	*40*	1827	*76*	2015	*76*	566	*511*	1105	*52*
age at reference date (years)												
< 30	0	*0*	16	*1*	0	*0*	7	*0*	0	*0*	8	*0*
30 – 39	634	*24*	685	*23*	315	*13*	335	*13*	240	*22*	438	*20*
40 – 49	838	*31*	923	*31*	800	*33*	879	*33*	362	*33*	718	*34*

50 – 59	1221	*45*	1284	*43*	1281	*54*	1397	*53*	500	*45*	949	*44*
> 59	0	*0*	49	*2*	0	*0*	31	*1*	0	*0*	24	*1*
highest education level												
University/high level technical/ postgraduate	1103	*41*	1225	*41*	847	*35*	978	*37*	465	*42*	931	*44*
comprehensive middle school [3]	380	*14*	519	*18*	403	*17*	554	*21*	117	*11*	226	*11*
vocational/upper secondary [3]	491	*18*	539	*18*	424	*18*	479	*18*	176	*16*	343	*16*
high school graduate/less [4]	719	*27*	674	*23*	722	*30*	638	*24*	344	*31*	637	*30*

[1] the same control could be matched to more than one case

[2] not included in analyses because of incomplete data, unmatched

[3] in Denmark, Finland, Germany, Italy, Norway, and Sweden

[4] in France, Germany, UK, Australia, Canada, Japan, and New Zealand

Short Communication

Association of allergic diseases and epilepsy with risk of glioma, meningioma and acoustic neuroma: results from the INTERPHONE international case-control study

Short title: Association of allergic diseases and epilepsy with brain tumours

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Abbreviations

IARC/WHO	International Agency for Research on Cancer / World Health Organisation
ICD-O	International Classification of Diseases for Oncology

CI	95% confidence interval
OR	Odds ratio

Declarations

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The authors confirm that they have no conflicts of interest.

Availability of data

Original data are not available as per ethical clearance and national data privacy legislations.

Code availability

Programming code of analysis used for the present paper can be obtained by contacting the corresponding author.

Authors' contributions

BS, MB and JS designed and jointly led the present project and drafted the manuscript. MM carried out the analysis. All other authors were also involved in the INTERPHONE study, its design, conduct and interpretation. EC was the overall coordinator of the INTERPHONE project. All authors reviewed and approved the manuscript.

Ethics approval

IARC Ethical approval was granted on 25 November 1999 (No ERC-Project 99-010). All study centers obtained national ethical approval.

Consent to participate

All participants of the INTERPHONE study filled in written informed consent.

Consent to publication

All authors critically reviewed and approved the final version of the manuscript.

Disclaimer

Where authors are identified as personnel of IARC/WHO, the authors alone are responsible for the views expressed in this article, and they do not necessarily represent the decisions, policy, or views of IARC/WHO.

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Abstract

We investigated the association of allergic diseases and epilepsy with risk of brain tumours, in Interphone, a 13-country case-control study. Data were obtained from 2693 glioma cases, 2396 meningioma cases, and 1102 acoustic neuroma cases and their 6321 controls. Conditional logistic regression models ~~for frequency matched data sets~~ were used to estimate pooled odds ratios (ORs) and their respective 95% confidence intervals (CIs), adjusted for education and time at interview. Reduced ORs were observed for glioma in relation to physician-diagnosed asthma (OR=0.73; CI 0.58-0.92), hay fever (OR 0.72; CI 0.61-0.86), and eczema (OR 0.78, CI 0.64-0.94), but not for meningioma or acoustic neuroma. Previous diagnosis of epilepsy was associated with an increased OR for glioma (2.94; CI 1.87-4.63) and for meningioma (2.12; CI 1.27-3.56), but not for acoustic neuroma. This large-scale case-control study adds to the growing evidence that people with allergies have a lower risk of developing glioma, but not meningioma or acoustic neuroma. It also supports clinical observations of epilepsy prior to the diagnosis of glioma and meningioma.

Key words: allergies, epilepsy, brain tumours, multicenter case-control study

Introduction

Epidemiological studies have consistently found an inverse association between a history of allergic diseases and risk of glioma, while results were conflicting for meningioma and acoustic neuroma [1-3]**.** Underlying biological mechanisms appear to be complex; however, there is agreement that immunologic functions play an important role in the development of brain tumours, and allergic diseases probably indicate an effective immunosurveillance system [1, 2]. Epilepsy or epileptic seizures can occur as early symptoms of brain tumors and it has been hypothesized that seizure susceptibility increases due to interaction between tumor cell metabolism and the neuronal network [4, 5].

Interphone is an international multi-center case-control study carried out in 13 countries and coordinated by IARC/WHO [6]. It focused on the association between mobile phone use and brain tumours, but data on allergic diseases and epilepsy were also collected. Here we report the results from the analysis of the pooled data set from the sixteen study centers on the associations between history of allergic diseases and epilepsy and risk of glioma, meningioma and acoustic neuroma.

Methods

The study population consists of incident, histologically or imaging-confirmed cases of glioma, meningioma and acoustic neuroma occurring between 2000 and 2004, 30-59 years old at diagnosis and their controls (sampled in frequency-matched manner and post-hoc individually

assigned with one per case for glioma and meningioma, two per case for acoustic neuroma). Controls were matched on age, sex, and study region (for details see [6, 7]).

Interviews were performed by trained interviewers, mainly using a computer-assisted questionnaire, either face-to-face (93.9 % cases, 99.5 % controls) or by telephone. Proxy interviews were conducted when the participant was too ill or deceased. This was the case for 336 glioma cases, 41 meningioma cases, 3 acoustic neuroma cases and 40 controls. The interview captured information on mobile phone use, ionizing and non-ionizing medical radiation exposures, socio-demographic factors and other potential risk factors for brain tumours. In addition, a history of various physician-diagnosed medical conditions, were asked, including diagnoses of asthma, hay fever, and eczema; which are conditions thought to reflect allergic reactions. Details were asked about the age at onset of these diseases, and for eczema the age when the symptoms stopped. Similar questions were asked for epilepsy.

Statistical approaches followed the strategy of all analyses of the Interphone study (for details see [6-7]). Conditional logistic regression models ~~for frequency-matched data sets~~ were used to estimate pooled odds ratios (ORs) and their 95% confidence intervals (CIs), adjusted for education and time interval between case and respective control interviews. Analyses were performed for each brain tumour type, and for men and women separately, or - if analysis was performed for men and women combined - adjusted for gender. Subgroup analyses were done separately for high-grade (type III-IV) and low-grade (type I and II) glioma, based on ICD-O morphological codes (details see [6, 7]).

Reference categories were defined as “never diagnosed with allergy” and ”never diagnosed with epilepsy”, respectively, as reported by the study subjects. Only diagnoses that occurred up to two years prior to the tumour diagnosis (cases) or reference date (controls; date of diagnosis of corresponding case) were included. Missing data was less than 5% for epilepsy and less than 1% for the allergies.

For each asthma, hay fever, and eczema, we created a binary variable (ever/never). We also investigated whether time since first diagnosis (< 10 years, 10 - 19 years, ≥20 years) or age at onset (< 10 years, 10 – 19 years, ≥20 years) was associated with the diseases. For eczema, we distinguished past and current rash. We also estimated ORs for one or more than one allergy compared with no allergy. Sensitivity analyses were performed by excluding proxy interviews and by including smoking as a potential confounder, but made no difference to the main results (data not shown).

Results

In total, the analyses included data from 2693 glioma cases (62.6% response rate), 2396 meningioma cases (76.9%) and 1102 acoustic neuroma cases (81.0%) and 6321 control subjects (44%). The distribution of cases and controls by selected demographic factors is presented in Supplementary Table 1. For all tumour types, educational level was slightly higher for controls than for cases.

For glioma, ORs below 1 were found for participants who were ever diagnosed with asthma (OR 0.73, CI 0.58-0.92), hay fever (OR 0.72, CI 0.61-0.86) or eczema (OR 0.78, CI 0.64-0.94), or "any allergy" (OR 0.71, CI 0.61-0.82) (Table 1). The result for eczema was driven by those with current rash. ORs were lowest when the allergies occurred less than ten years before glioma tumour diagnosis, and for those whose allergies started in adulthood. Subdivision into high grade and low grade glioma showed that the decrease was driven by the results for high-grade glioma (Table 1). For meningioma, no association was seen in relation to asthma (OR 0.91, CI 0.72-1.14) or to hay fever (OR 0.91, CI 0.76-1.10), but eczema showed a slightly lower risk (OR 0.84, CI 0.70-1.02), that was more pronounced for those with current rash (OR 0.76; CI 0.60-0.95) (Table 1). For both tumour types there was little difference in ORs between men and women, but for hay fever and eczema the ORs for men were somewhat lower (Table 2).

For acoustic neuroma no association was found with asthma (OR 1.02, CI 0.75-1.37), hay fever (OR 0.91, CI 0.72-1.14), or eczema (OR 1.02, CI 0.78-1.32), overall and by time since start of the allergy or by age at onset. The results were similar for men and women (Tables 1 and 2).

A prior diagnosis of epilepsy was associated with an increased OR for glioma (OR 2.94, CI 1.87-4.63) and for meningioma (OR 2.12, CI 1.27-3.56) (Table1). Subgroup analyses for glioma and meningioma and epilepsy were based on small numbers (Tables 1 and 2). However, for both glioma and meningioma, sex-specific analyses revealed higher risks for men than for women. The OR was higher for low-grade glioma (OR 5.71, CI 2.48-13.1) compared with high-grade glioma (OR 2.01, CI 1.14-3.54). For both glioma and meningioma, the highest ORs were seen for adult-onset epilepsy, and for subjects whose epilepsy was diagnosed less than 10 years before

the reference date. ORs were not increased for acoustic neuroma (Table 1), however, analyses were based on small numbers of subjects with epilepsy.

Discussion

These results presented were based on data from all Interphone study centres [6, 7]. Some differences in results published from single or smaller groups of study centres [e.g. 3, as most recent], may be due to chance or to differences in participation rates, prevalence of specific diseases or other factors.

Allergic diseases

We found inverse associations of asthma, hay fever and eczema with risk of glioma, especially for high-grade glioma, for both men and women. Allergic diseases diagnosed closer to the diagnosis of the high-grade glioma (less than 10 years) were associated with lower ORs than those diagnosed earlier and at early ages. Our findings are consistent with previous studies, a recent meta-analysis [8] and review [9]. Overall, no association was seen between low-grade glioma, meningioma, and acoustic neuroma with any of the three allergic diseases [1]. Decreased ORs were observed, however, for low grade glioma and for meningioma for those who at time of interview reported current eczema.

Prospective studies found lower levels of total or respiratory-specific immunoglobulin IgE, a biomarker of allergy, in glioma patients, strengthening our observation of an inverse

association [1, 8]. The underlying biogenetic mechanism is not fully understood. The immediate hypersensitivity reactions of these three allergies are mediated by IgE, and this may be influenced by preclinical tumours. Further investigations of immunologic mechanisms, for example in the immunosurveillance system, and investigations of germline SNPs or genetic risk factors are needed for better understanding of the mechanism [2].

History of Epilepsy

In line with earlier epidemiological studies and clinical observations, we found elevated ORs of glioma and meningioma in relation to past epilepsy with the highest ORs for low-grade glioma, a finding also described by other studies [4]. No association was seen between history of epilepsy and acoustic neuroma but numbers of subjects were small. Epilepsy and epileptic seizures prior, but close to the diagnosis of glioma or meningioma are known to be important symptoms of brain tumours as an early warning sign and a prognostic factor for survival [5]. Different hypotheses concerning the epileptogenesis in tumour cells and peritumoral cells have been discussed, e.g. that an aberrant tumour cell metabolism may influence the neuronal network leading to seizures [4, 10].

Strengths and Limitations

This is to our knowledge the largest ever case-control study on this topic. With all centres following the same study protocol, no compromises had to be made when pooling the data. Participation proportions in cases (glioma 63%, meningioma 77% and acoustic neuroma 81%) were high and the distribution of cases by sex and age was as to be expected for the respective

tumours types. For glioma, proxy interviews were used for 12% of cases, but excluding them had little effect on the results. Main limitations were the low response proportion among controls and the fact that all data on medical diagnoses were based on self-reports of a physician diagnosis, leading to concerns about potential selection and recall bias.

Selection bias was of particular concern as response rates did somewhat differ by education (lower with shorter education) and prevalence of allergies may also differ by education; but in fact the association between allergies and education was weak (data not shown). Odds ratios with or without adjustment for education did hardly differ. Stratified analysis by education did not show any differences for glioma. For meningioma, the odds ratios differed slightly between groups, but were close to 1 for any educational level. Hence we conclude that the inverse association for glioma is not due to selection bias but the minor decrease in odds ratios for meningioma may well be.

Conclusions

Findings from this large-scale, international case-control study with a representative distribution of cases for the respective tumour types, add to the growing evidence that people with allergies have a lower risk of glioma than those without allergies, especially for high-grade glioma, but not for meningioma or acoustic neuroma. It also confirms the association between epilepsy and glioma and meningioma, most likely due to epilepsy being a symptom for a sizeable proportion of these tumours.

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Table 1: Association between tumour and allergy or epilepsy, by time since start[1] and age at onset[2]

	Glioma		low grade glioma		high grade glioma		meningioma		acoustic neuroma	
	cases/ controls	OR (95% CI 95%)	cases/ controls	OR (95% CI 95%)	cases/ controls	OR (95% CI 95%)	cases/ controls	OR (95% CI 95%)	cases/ controls	OR (95% CI 95%)
Asthma										
Ever/never										
never	2453/2630	1.00	751/797	1.00	1678/1805	1.00	2161/2377	1.00	1001/1928	1.00
ever	220/303	0.73 (0.58-0.92)	82/107	0.89 (0.60-1.34)	137/196	0.65 (0.49-0.87)	228/263	0.91 (0.72-1.14)	99/204	1.02 (0.75-1.37)
Time since start										
never	2453/2630	1.00	751/797	1.00	1678/1805	1.00	2161/2377	1.00	1001/1928	1.00
< 10 years	49/92	0.67 (0.44-1.02)	25/29	1.05 (0.53-2.08)	23/63	0.47 (0.26-0.85)	66/73	0.91 (0.62-1.34)	34/70	0.99 (0.59-1.64)
10-19 years	37/60	0.53 (0.32-0.88)	18/25	0.80 (0.37-1.74)	19/35	0.36 (0.17-0.76)	54/51	1.18 (0.71-1.94)	13/32	0.62 (0.28-1.37)
20 + years	134/151	0.85 (0.63-1.15)	39/53	0.84 (0.48-1.49)	95/98	0.84 (0.59-1.21)	108/139	0.83 (0.61-1.13)	52/102	1.20 (0.80-1.80)
Age at onset										
never	2453/2630	1.00	751/797	1.00	1678/1805	1.00	2161/2377	1.00	1001/1928	1.00
child (0-9)	93/103	0.80 (0.56-1.15)	22/38	0.66 (0.33-1.30)	71/65	0.87 (0.57-1.33)	53/82	0.57 (0.36-0.89)	36/61	1.30 (0.79-2.15)
young (10-19)	39/43	0.95 (0.55-1.64)	17/20	0.83 (0.36-1.92)	22/23	1.09 (0.54-2.23)	39/33	1.37 (0.79-2.40)	15/30	1.29 (0.60-2.78)
adult (20+)	88/157	0.62 (0.45-0.86)	43/49	1.09 (0.64-1.86)	44/108	0.40 (0.26-0.63)	136/148	1.00 (0.75-1.33)	48/113	0.81 (0.54-1.23)
Hay Fever										
Ever/never										
never	2251/2365	1.00	684/713	1.00	1546/1628	1.00	2006/2162	1.00	895/1720	1.00
ever	410/558	0.72 (0.61-0.86)	150/194	0.86 (0.63-1.15)	256/360	0.67 (0.54-0.84)	370/465	0.91 (0.76-1.10)	201/402	0.91 (0.72-1.14)
Time since start										
never	2251/2365	1.00	684/713	1.00	1546/1628	1.00	2006/2162	1.00	895/1720	1.00
< 10 years	80/117	0.67 (0.47-0.96)	30/41	0.99 (0.57-1.73)	49/76	0.53 (0.33-0.85)	82/105	0.96 (0.66-1.40)	54/99	0.95 (0.61-1.48)
10 – 19 years	75/126	0.56 (0.39-0.79)	28/48	0.52 (0.27-0.99)	46/76	0.57 (0.36-0.89)	83/109	0.86 (0.61-1.21)	41/92	0.77 (0.49-1.22)
20 + years	255/315	0.81 (0.66-1.01)	92/105	0.95 (0.65-1.38)	161/208	0.77 (0.59-1.01)	205/251	0.92 (0.73-1.16)	106/211	0.95 (0.71-1.28)
Age at onset (years)										
Never	2251/2365	1.00	684/713	1.00	1546/1628	1.00	2006/2162	1.00	895/1720	1.00
child (0-9)	89/107	0.84 (0.59-1.21)	34/39	0.99 (0.55-1.78)	55/67	0.77 (0.48-1.24)	58/68	1.04 (0.68-1.58)	32/64	0.96 (0.58-1.59)

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~~young (~~10-19~~)~~	131/174	0.75 (0.56-1.00)	51/69	0.80 (0.50-1.28)	79/103	0.77 (0.53-1.12)	106/128	0.85 (0.63-1.16)	59/122	0.95 (0.64-1.39)
~~adult (~~20+~~)~~	190/277	0.67 (0.53-0.84)	65/86	0.84 (0.55-1.28)	122/190	0.60 (0.45-0.80)	206/269	0.92 (0.72-1.16)	110/216	0.87 (0.64-1.18)
Eczema										
Ever/never										
never	2350/2491	1.00	723/762	1.00	1605/1707	1.00	2064/2207	1.00	954/1791	1.00
ever	313/435	0.78 (0.64-0.94)	110/145	0.73 (0.51-1.03)	200/284	0.78 (0.61-0.98)	316/426	0.84 (0.70-1.02)	145/333	1.02 (0.78-1.32)
Time since start (years)										
never	2350/2491	1.00	723/762	1.00	1605/1707	1.00	2064/2207	1.00	954/1791	1.00
< 10 ~~years~~	55/108	0.58 (0.39-0.85)	21/41	0.48 (0.25-0.92)	34/65	0.66 (0.40-1.08)	58/97	0.81 (0.55-1.21)	26/81	0.79 (0.46-1.37)
10 -19 ~~years~~	69/83	0.91 (0.62-1.34)	24/23	0.79 (0.37-1.67)	43/59	0.87 (0.54-1.40)	66/73	1.03 (0.68-1.55)	32/70	1.09 (0.64-1.87)
20 + ~~years~~	189/244	0.82 (0.65-1.05)	65/81	0.85 (0.56-1.31)	123/160	0.79 (0.59-1.07)	192/256	0.81 (0.64-1.02)	87/182	1.09 (0.79-1.51)
Age at onset (years)										
Never	2350/2491	1.00	723/762	1.00	1605/1707	1.00	2064/2207	1.00	954/1791	1.00
~~child (~~0-9~~)~~	93/125	0.75 (0.53-1.05)	35/51	0.75 (0.44-1.27)	57/70	0.76 (0.48-1.21)	89/108	0.81 (0.59-1.13)	44/92	0.93 (0.60-1.44)
~~young (~~10-19~~)~~	77/87	1.07 (0.74-1.54)	29/25	1.10 (0.55-2.19)	47/62	0.98 (0.63-1.55)	67/97	0.83 (0.57-1.21)	33/65	1.36 (0.80-2.31)
~~adult (~~20+~~)~~	143/223	0.68 (0.53-0.89)	46/69	0.57 (0.34-0.94)	96/152	0.70 (0.51-0.97)	160/221	0.87 (0.67-1.12)	68/176	0.96 (0.67-1.37)
Past/current										
Never	2348/2485	1.00	722/761	1.00	1604/1702	1.00	2060/2200	1.00	954/1784	1.00
Past	127/138	1.01 (0.74-1.37)	47/44	1.01 (0.58-1.77)	79/93	0.95 (0.65-1.39)	125/135	1.03 (0.75-1.40)	55/107	1.13 (0.73-1.74)
Current	179/291	0.67 (0.53-0.85)	61/98	0.63 (0.42-0.95)	116/188	0.68 (0.51-0.91)	184/283	0.76 (0.60-0.95)	87/218	0.96 (0.71-1.32)
Allergies										
Any allergy										
None	1903/1894	1.00	568/565	1.00	1316/1309	1.00	1661/1731	1.00	757/1393	1.00
at least one	721/989	0.71 (0.61-0.82)	253/327	0.78 (0.60-1.01)	462/654	0.67 (0.56-0.80)	699/878	0.86 (0.74-1.00)	336/715	0.91 (0.75-1.11)
Time since start (years)										
Never	1903/1894	1.00	568/565	1.00	1316/1309	1.00	1661/1731	1.00	757/1393	1.00
< 10 ~~years~~	126/229	0.56 (0.42-0.74)	47/74	0.68 (0.42-1.09)	78/154	0.50 (0.35-0.71)	135/189	0.77 (0.58-1.03)	81/178	0.85 (0.59-1.21)
10 – 19 ~~years~~	137/196	0.65 (0.49-0.86)	51/68	0.63 (0.38-1.03)	83/126	0.61 (0.43-0.87)	144/177	0.84 (0.63-1.12)	65/145	0.81 (0.55-1.17)
20 + ~~years~~	458/564	0.79 (0.66-0.94)	155/185	0.88 (0.65-1.20)	301/374	0.75 (0.61-0.93)	420/512	0.89 (0.75-1.06)	190/392	0.98 (0.77-1.24)
Age at onset (years)										

Never	1903/1894	1.00	568/565	1.00	1316/1309	1.00	1661/1731	1.00	757/1393	1.00
~~child (~~0-9~~)~~	215/281	0.71 (0.56-0.90)	72/104	0.77 (0.52-1.15)	142/172	0.69 (0.51-0.94)	171/209	0.83 (0.64-1.07)	87/177	0.95 (0.68-1.32)
~~young (~~10-19~~)~~	193/233	0.84 (0.65-1.07)	76/82	0.89 (0.57-1.38)	115/150	0.80 (0.59-1.10)	169/202	0.93 (0.72-1.20)	82/167	1.06 (0.75-1.49)
~~adult (~~20+~~)~~	313/475	0.65 (0.53-0.78)	105/141	0.73 (0.51-1.04)	205/332	0.60 (0.47-0.76)	359/467	0.84 (0.70-1.02)	167/371	0.83 (0.64-1.07)
Epilepsy										
Ever/never										
Never	2499/2811	1.00	775/882	1.00	1701/1902	1.00	2276/2532	1.00	1061/2057	1.00
Ever	101/33	2.94 (1.87-4.63)	48/10	5.71 (2.48-13.1)	52/23	2.01 (1.14-3.54)	61/32	2.12 (1.27-3.56)	17/26	1.44 (0.68-3.07)
Time since start (years)										
Never	2499/2811	1.00	775/882	1.00	1701/1902	1.00	2276/2532	1.00	1061/2057	1.00
< 10 ~~years~~	52/7	8.44 (3.28-21.7)	25/2	21.7 (2.89-163)	26/5	5.09 (1.66-15.6)	21/5	6.73 (1.90-23.9)	1/8	0.16 (0.01-1.84)
10 – 19 ~~years~~	21/4	3.62 (1.09-12.0)	14/3	3.64 (0.91-14.5)	7/1	3.38 (0.38-30.4)	12/2	4.37 (0.83-22.9)	5/2	15.7 (1.00-242)
20 + ~~years~~	28/22	1.28 (0.67-2.46)	9/5	2.15 (0.50-9.23)	19/17	1.09 (0.51-2.32)	28/25	1.32 (0.71-2.43)	11/16	1.70 (0.68-4.28)
Age at onset (years)										
Never	2499/2811	1.00	775/882	1.00	1701/1902	1.00	2276/2532	1.00	1061/2057	1.00
~~child (~~0-9~~)~~	9/10	0.97 (0.31-2.99)	5/3	3.52 (0.33-37.8)	4/7	0.63 (0.16-2.45)	14/13	1.24 (0.51-3.02)	3/5	1.38 (0.32-6.02)
~~young (~~10-19~~)~~	15/11	0.94 (0.38-2.33)	7/3	1.72 (0.39-7.57)	8/8	0.61 (0.18-2.02)	10/5	1.52 (0.45-5.10)	6/8	2.66 (0.72-9.76)
~~adult (~~20+~~)~~	77/12	6.61 (3.30-13.2)	36/4	10.68 (3.15-36)	40/8	4.89 (2.07-11.6)	37/14	3.35 (1.58-7.10)	8/13	0.90 (0.27-2.98)

[1]*Between first diagnosis by a physician and two years before tumour diagnosis (cases) or reference date (controls)*

[2]*Reference category (never): no diagnosis of disease up to two years before tumour diagnosis (cases) or reference date (controls); adjusted for education and time at interview; cases and controls answering "don't know" for a disease or having missing values in the adjustment variables were excluded from analyses*

Table 2: Association between tumour and allergy or epilepsy, by gender[1]

	glioma - men		glioma - women		meningioma - men		meningioma - women		acoustic neuroma – men		acoustic neuroma – women	
	cases/ controls	OR (95% CI 95%)	cases/ controls	OR (95% CI 95%)	cases/ controls	OR (95% CI 95%)	cases/ controls	OR (95% CI 95%)	cases/ controls	OR (95% CI 95%)	cases/ controls	OR (95% CI 95%)
Asthma												
never	1477/1590	1.00	976/1040	1.00	519/575	1.00	1642/1802	1.00	488/943	1.00	513/985	1.00
ever	127/165	0.75 (0.55-1.02)	93/138	0.71 (0.50-1.02)	45/52	1.00 (0.61-1.63)	183/211	0.88 (0.68-1.14)	47/87	1.02 (0.63-1.63)	52/117	0.95 (0.64-1.42)
Hay Fever												
never	1360/1428	1.00	891/937	1.00	483/533	1.00	1523/1629	1.00	440/843	1.00	455/877	1.00
ever	234/319	0.67 (0.53-0.85)	176/239	0.75 (0.58-0.98)	81/95	0.87 (0.58-1.31)	289/370	0.91 (0.74-1.12)	93/181	0.93 (0.65-1.32)	108/221	0.85 (0.62-1.16)
Eczema												
never	1446/1536	1.00	904/955	1.00	521/552	1.00	1543/1655	1.00	473/898	1.00	481/893	1.00
ever	150/214	0.74 (0.56-0.97)	163/221	0.80 (0.61-1.05)	44/78	0.59 (0.36-0.94)	272/348	0.91 (0.74-1.12)	62/129	1.01 (0.65-1.55)	83/204	1.04 (0.74-1.45)
Any allergy												
none	1174/1176	1.00	729/718	1.00	423/445	1.00	1238/1286	1.00	378/708	1.00	379/685	1.00
1 and more	400/549	0.66 (0.54-0.80)	321/440	0.75 (0.6-0.94)	137/177	0.77 (0.56-1.06)	562/701	0.88 (0.74-1.04)	153/309	0.93 (0.69-1.27)	183/406	0.87 (0.67-1.14)
Epilepsy												
never	1493/1675	1.00	1006/1136	1.00	530/603	1.00	1746/1929	1.00	514/989	1.00	547/1068	1.00
ever	62/20	3.71 (2.02-6.82)	39/13	2.37 (1.16-4.81)	20/5	5.46 (1.67-17.8)	41/27	1.55 (0.86-2.79)	8/11	2.23 (0.65-7.66)	9/15	1.26 (0.46-3.43)

[1]*Reference category (never): no symptoms of disease up to two years before tumour diagnosis (cases) or reference date (controls); adjusted for education and time at interview; cases and controls answering "don't know" for a disease or had missing values in the adjustment variables were excluded from analyses*

Supplementary table: Description of the study population for the analyses of allergic conditions and epilepsy. Interphone Study Group

	Glioma Cases		meningioma cases		acoustic neuroma cases		controls[1]	
	n	%	n	%	n	%	n	%
Status of interview								
total ascertained	4301	100	3115	100	1361	100	14354	100
not interviewed	1536	36	690	22	240	18	6696	47
interviewed	2765	64	2425	78	1121	82	7658	53
Reasons for exclusion								
not interviewed	1536	*100*	690	*100*	240	*100*	6696	*100*
refused ~~self~~	*470*	*31*	*339*	*49*	*148*	*62*	*4303*	*64*
doctor refusal	*198*	*13*	*69*	*10*	*23*	*10*	*126*	*2*
dead or too ill	*637*	*42*	*66*	*10*	*5*	*2*	*49*	*1*
language problems	*34*	*2*	*50*	*7*	*12*	*5*	*133*	*2*
unable to trace	*157*	*10*	*137*	*20*	*46*	*19*	*1819*	*27*
other reasons	*40*	*3*	*29*	*4*	*6*	*3*	*266*	*4*
Interviewed but excluded[2]	72		29		19		1337	

	Glioma				meningioma				acoustic neuroma			
	cases		controls		cases		controls		cases		Controls	
	n	*%*	**n**	*%*	**n**	*%*	**n**	*%*	**n**	*%*	**n**	*%*
inclusion in analyses	**2693**	*100*	**2957**	*100*	**2396**	*100*	**2649**	*100*	**1102**	*100*	**2137**	*100*
Men	1614	*60*	1768	*60*	569	*24*	634	*24*	536	*49*	1032	*48*
women	1079	*40*	1189	*40*	1827	*76*	2015	*76*	566	*511*	1105	*52*
age at reference date (years)												
< 30 ~~years~~	0	*0*	16	*1*	0	*0*	7	*0*	0	*0*	8	*0*
30 - 39 ~~years~~	634	*24*	685	*23*	315	*13*	335	*13*	240	*22*	438	*20*
40 - 49 ~~years~~	838	*31*	923	*31*	800	*33*	879	*33*	362	*33*	718	*34*

50 - 59 years	1221	*45*	1284	*43*	1281	*54*	1397	*53*	500	*45*	949	*44*
> 59 years	0	*0*	49	*2*	0	*0*	31	*1*	0	*0*	24	*1*
highest education level												
Uuniversity/high level technical/ postgraduatepostgrad	1103	*41*	1225	*41*	847	*35*	978	*37*	465	*42*	931	*44*
comprehensive middle school [3]	380	*14*	519	*18*	403	*17*	554	*21*	117	*11*	226	*11*
vocational/upper secondary [3]	491	*18*	539	*18*	424	*18*	479	*18*	176	*16*	343	*16*
high school graduate/less [4]	719	*27*	674	*23*	722	*30*	638	*24*	344	*31*	637	*30*

[1] *the same control could be matched to more than one case*

[2] *nonparticipating not included in analyses because of incomplete data, unmatched*

[3] *in Denmark, Finland, Germany, Italy, Norway, and Sweden*

[4] *in France, Germany, UK, Australia, Canada, Japan, and New Zealand*

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Dear Editor,

we are very grateful for the helpful comments of the reviewer. Please find our answer below.

COMMENTS TO THE AUTHOR:

Reviewer #1: EJEP-D-21-01240
The authors present a very well written manuscript. With the amount of sites and coauthors, one can only imagine the coordination work that was necessary before submission.

Reviewer:

MAJOR POINT

Selection Bias
The prevalence of allergic diseases, medical diagnosis, and self-report of allergic diseases by individuals is social class-dependent in many nations of Europe.
The low response in the control group (44%) was associated with oversampling of the higher social class. Thus, the control group overestimates the exposure prevalence of interest (allergic diseases). This bias may at least partly explain the odds ratio of < 1 for allergic diseases.
The authors address this selection bias by statistically adjusting their analyses for education. Please explain how the authors removed the selection bias from the data. I would rather have expected a bias analysis (at least deterministic, preferably probabilistic) for the selection bias.

Our answer:

We like to thank the reviewer for raising this very important point.

Indeed, we observed differences in the response rates by educational level, minor in cases and more so in controls. We observed however only weak associations between prevalence of different allergies and educational level. Taking these two together, we believe there is no major impact by selection bias.

We have investigated this in different separate analyses. As already reported, adjustment for educational level did not change any results. Stratified analyses by educational level did not change the results for glioma. For meningioma the risk differed slightly between educational levels, however was still close to 1.00 for any educational level. However, any decreased odd ratio may be explained to a small extent by selection bias.

We have described this in the discussion (page 18).

Reviewer:

MINOR POINTS

The authors first state that they have performed frequency matching. Then on page 14 they state "Only diagnoses that occurred up to two years prior to the tumor diagnosis (cases) or reference date (controls; date of diagnosis of corresponding case)". Here it sounds like an individual matching was performed. I do not understand this correctly.

Our answer:

We thank the reviewer for this comment as this was confusing. To make a long story short, controls were drawn in a frequency-matched way but post-hoc individually assigned to cases. This was necessary for the mobile phone-related approach as prevalence changed rapidly over time, and we kept the approach for all other Interphone related analyses. We added this explanation in the Methods.

Our procedure for matching is described in more detail in the cited Interphone Paper (Ref 6). Briefly: All 16 study centres selected there controls randomly from the source population. Our study-design called for controls to be individually- or frequency-matched to cases, with 1:1

matching for glioma and meningioma (except Germany which has done 1:2) and 1:2 for acoustic neuroma. Controls were matched on year of birth (within 5-year categories), sex and study region.

Canada-Ottawa, Vancouver, France, Israel, Japan, new-Zealand and UK-North matched individually, the other countries used first frequency matching and conducted individual matching post-hoc. Post-hoc matched controls were only those who were interviewed as close as possible in time to the respected case interview (about 3 month) (reference date), in addition to the general matching criteria. For the analyses we stratified for age, sex and study region for different reasons depended on the topic.

Therefore we used conditional logistic regression analyses for individual and post-hoc matching.

Reviewer:

The table layout of tables 1-2 is not comfortable (slashes between numbers of people, etc.).

Our answer:

We improved the layout of the tables. We left the slashes between cases and controls as we felt this helps for clarity, but removed them otherwise. Also we removed abbreviations and checked for consistency.

With best regards, sincerely,

Dr. Brigitte Schlehofer

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Disclosure of potential conflicts of interest

Authors must disclose all relationships or interests that could have direct or potential influence or impart bias on the work. Although an author may not feel there is any conflict, disclosure of all relationships and interests provides a more complete and transparent process, leading to an accurate and objective assessment of the work. Awareness of real or perceived conflicts of interest is a perspective to which the readers are entitled. This is not meant to imply that a financial relationship with an organization that sponsored the research or compensation received for consultancy work is inappropriate. For examples of potential conflicts of interests *that are directly or indirectly related to the research please* visit:
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☒ I have no potential conflict of interest.

Category of disclosure	Description of Interest/Arrangement

Article title Association of allergic dieases and epilepsy with risk of glioma, meningioma and AN

Manuscript No. (if you know it) EJEP-D-21-01240

Author name Joachim Schüz

Are you the corresponding author? ☒ Yes ☐ No

Herewith I confirm that the information provided is accurate.

Author signature Joachim Schüz Digitally signed by Joachim Schüz DN: cn=Joachim Schüz, o=IARC, ou, email=schuzj@iarc.fr, c=FR Date: 2021.10.04 18:03:01 +02'00' Date 4 October 2021