



HAL
open science

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

Brigitte Schlehofer, Maria Blettner, Monika Moissonnier, Isabelle Deltour, Graham G. Giles, Bruce Armstrong, Jack Siemiatycki, Marie-Elise Parent, Daniel Krewski, Christoffer Johansen, et al.

► To cite this version:

Brigitte Schlehofer, Maria Blettner, Monika Moissonnier, Isabelle Deltour, Graham G. Giles, et al.. Association of allergic diseases and epilepsy with risk of glioma, meningioma and acoustic neuroma: results from the INTERPHONE international case-control study. *European Journal of Epidemiology*, 2022, 37 (5), pp.503-512. 10.1007/s10654-022-00843-y . hal-04060209

HAL Id: hal-04060209

<https://hal.science/hal-04060209>

Submitted on 6 Apr 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



UNIVERSITY OF LEEDS

This is a repository copy of *Association of allergic diseases and epilepsy with risk of glioma, meningioma and acoustic neuroma: results from the INTERPHONE international case-control study*.

White Rose Research Online URL for this paper:

<https://eprints.whiterose.ac.uk/183589/>

Version: Accepted Version

Article:

Schlehofer, B, Blettner, M, Moissonnier, M et al. (25 more authors) (2022) Association of allergic diseases and epilepsy with risk of glioma, meningioma and acoustic neuroma: results from the INTERPHONE international case-control study. *European Journal of Epidemiology*, 37 (5). pp. 503-512. ISSN 0393-2990

<https://doi.org/10.1007/s10654-022-00843-y>

© Springer Nature B.V. 2022. This is an author produced version of an article, published in *European Journal of Epidemiology*. Uploaded in accordance with the publisher's self-archiving policy.

Reuse

Items deposited in White Rose Research Online are protected by copyright, with all rights reserved unless indicated otherwise. They may be downloaded and/or printed for private study, or other acts as permitted by national copyright laws. The publisher or other rights holders may allow further reproduction and re-use of the full text version. This is indicated by the licence information on the White Rose Research Online record for the item.

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.



eprints@whiterose.ac.uk
<https://eprints.whiterose.ac.uk/>

European Journal of Epidemiology

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

Manuscript Number:	EJEP-D-21-01240R1
Full Title:	Association of allergic diseases and epilepsy with risk of glioma, meningioma and acoustic neuroma: results from the INTERPHONE international case-control study
Article Type:	Short Communication
Keywords:	allergies; epilepsy; brain tumours; multicenter case-control study
Corresponding Author:	Joachim Schüz IARC: International Agency for Research on Cancer FRANCE
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	IARC: International Agency for Research on Cancer
Corresponding Author's Secondary Institution:	
First Author:	Joachim Schüz
First Author Secondary Information:	
Order of Authors:	Joachim Schüz Brigitte Schlehofer Maria Blettner Monika Moissonnier Isabelle Deltour Graham G Giles Bruce Armstrong Jack Siemiatycki Marie-Elise Parent Daniel Krewski Christoffer Johansen Anssi Auvinen Anna Lahkola Martine Hours Gabriele Berg-Beckhoff Siegal Sadetzki Susanna Lagorio Toru Takebayashi Naohito Yamaguchi Alistair Woodward Angus Cook Tore Tynes

	Lars Klaboe
	Maria Feychting
	Richard Feltbower
	Anthony Swerdlow
	Minouk Schoemaker
	Elisabeth Cardis
Order of Authors Secondary Information:	
Funding Information:	
Abstract:	<p>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.</p>
Response to Reviewers:	<p>Dear Editor, we are very grateful for the helpful comments of the reviewer. Please find our answer below.</p> <p>COMMENTS TO THE AUTHOR:</p> <p>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.</p> <p>Reviewer: MAJOR POINT</p> <p>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.</p>

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 their 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 months) (reference date), in addition to the general matching criteria. For the analyses we stratified for age, sex and study region for different reasons depending 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

[Click here to view linked References](#)

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

Brigitte Schlehofer¹, Maria Blettner², Monika Moissonnier³, Isabelle Deltour³, Graham G Giles^{4,5,6}, Bruce Armstrong, Jack Siemiatycki⁸, Marie-Elise Parent⁹, Daniel Krewski¹⁰, Christoffer Johansen¹¹, Anssi Auvinen^{12,13}, Anna Lahkola¹³, Martine Hours¹⁴, Gabriele Berg-Beckhoff¹⁵, Siegal Sadetzki^{16,17,18}, Susanna Lagorio¹⁹, Toru Takebayashi²⁰, Naohito Yamaguchi²¹, Alistair Woodward²², Angus Cook²³, Tore Tynes²⁴, Lars Klaboe²⁵, Maria Feychting²⁶, Richard Feltbower²⁷, Anthony Swerdlow²⁸, Minouk Schoemaker²⁸, Elisabeth Cardis^{29,30,31}, Joachim Schüz³

¹ private: Leimen, Germany; retired, former: Unit of Environmental Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany

² Institute of Medical Biostatistics, Epidemiology and Informatics, University of Mainz, Germany

³ International Agency for Research on Cancer (IARC/WHO), Environment and Lifestyle Epidemiology Branch, Lyon, France

⁴ Cancer Epidemiology Division, Cancer Council Victoria, Melbourne, Victoria, Australia

⁵ Centre for Epidemiology and Biostatistics, School of Population and Global Health, University of Melbourne, Parkville, Victoria, Australia

⁶ Precision Medicine, School of Clinical Sciences at Monash Health, Monash University, Clayton, Victoria, Australia

⁷ School of Public Health, University of Sydney, Sydney, Australia

⁸ University of Montreal, Montreal, Canada

⁹ Institut national de la recherche scientifique (INRS), Laval, Canada

¹⁰ McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, Ottawa, Canada

¹¹ Center for Surgery and Cancer, Rigshospitalet, Copenhagen, Denmark

¹² Tampere University, Faculty of Social Sciences, Finland

¹³ STUK Radiation and Nuclear Safety Authority, Environmental Radiation Surveillance, Helsinki, Finland

¹⁴ Université Lyon 1, IFSTTAR, UMRESTTE, Bron, France

¹⁵ Unit for Health Promotion Research, Department of Public Health, and Hospital South West Jutland Esbjerg; University of Southern Denmark, Denmark

- ¹⁶ Cancer & Radiation Epidemiology Unit, Gertner Institute for Epidemiology & Health Policy Research, Sheba Medical Center, Tel-Hashomer, Israel
- ¹⁷ Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
- ¹⁸ Ministry of Health, Jerusalem, Israel
- ¹⁹ Department of Oncology and Molecular Medicine, Istituto Superiore di Sanità, Rome, Italy
- ²⁰ Department of Preventive Medicine and Public Health, Keio University School of Medicine, Tokyo, Japan
- ²¹ Department of Public Health, Tokyo Women's Medical University School of Medicine, Tokyo, Japan
- ²² School of Population Health, University of Auckland, Auckland, New Zealand
- ²³ Population and Global Health, The University of Western Australia, Perth, WA, Australia
- ²⁴ National Institute of Occupational Health, Oslo, Norway
- ²⁵ Norwegian Radiation Protection Authority, Østerås; The Cancer Registry of Norway, Oslo, Norway
- ²⁶ Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
- ²⁷ School of Medicine, University of Leeds, UK
- ²⁸ Institute of Cancer Research, Sutton, UK
- ²⁹ Barcelona Institute of Global Health (ISGlobal), Barcelona, Spain
- ³⁰ University Pompeu Fabra, Barcelona, Spain
- ³¹ CIBER Epidemiologia y Salud Pública, Madrid, Spain

ORCID-ID

Joachim Schüz <http://orcid.org/0000-0001-9687-2134>
Jack Siemiatycki <https://orcid.org/0000-0002-9042-8582>
Maria Feychting <https://orcid.org/0000-0002-5101-0060>
Susanna Lagorio <https://orcid.org/0000-00001-8883-8745>
Elisabeth Cardis <https://orcid.org/0000-0003-0999-6839>
Gabriele Berg-Beckhoff <https://orcid.org/0000-0003-1614-938X>
Isabelle Deltour <https://orcid.org/0000-0002-6602-6292>
Marie-Elise Parent <https://orcid.org/0000-0002-4196-3773>
Graham Giles <https://orcid.org/0000-0003-4946-9099>
Anssi Auvinen <https://orcid.org/0000-0003-1125-4818>

Corresponding author: Joachim Schüz, schuzj@iarc.fr

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

Funding:

There was no particular grant for the present work with the core writing group contributing from their regular positions (BS, MB, MM, JS), with some funding for travel and meetings provided by the International Agency for Research on Cancer (IARC/WHO).

The INTERPHONE study was supported by funding from the European Fifth Framework Program, 'Quality of Life and Management of Living Resources' (contract QLK4-CT-1999901563) and the International Union against Cancer (UICC). The UICC received funds for this purpose from the Mobile Manufacturers' Forum and GSM Association. Provision of funds to the INTERPHONE study investigators via the UICC was governed by agreements that guaranteed INTERPHONE's complete scientific independence. The terms of these agreements are publicly available at <https://interphone.iarc.fr/funding>

The Australian centre was supported by the Australian National Health and Medical Research Council (EME Grant 219129) with funds originally derived from mobile phone service licence fees. Cancer Council NSW and Cancer Council Victoria provided most of the infrastructure for the project in Australia.

The Canada – Montreal study was primarily funded by a grant from the Canadian Institutes of Health Research (project 15 MOP-42525). Additionally, Dr Siemiatycki's research team was partly funded by the Canada Research Chair programme and by the Guzzo-CRS Chair in Environment and Cancer. Dr Parent had a salary award from the Fonds de la recherche en santé du Québec.

The Canadian centres in Ottawa/Vancouver were supported by a university–industry partnership grant from the Canadian Institutes of Health Research (CIHR), the latter including partial support from the Canadian Wireless Telecommunications Association. The CIHR university–industry partnerships program also includes provisions that ensure complete scientific independence of the investigators. D. Krewski is the Natural Sciences and Engineering Research Council of Canada Chair in Risk Science at the University of Ottawa.

Additional funding for the study in France was provided by l'Association pour la Recherche sur le Cancer (ARC) [Contrat No. 5142] and three network operators (Orange, SFR, Bouygues Télécom). The funds provided by the operators represented 5% of the total cost of the French study and were governed by contracts guaranteeing the complete scientific independence of the investigators.

The Finnish Interphone study received additional national funding from Emil Aaltonen Foundation and Academy of Finland (Grant No. 80921).

The German Interphone study received additional national funding from the "Deutsches Mobilfunkforschungsprogramm [German Mobile Phone Research Program]" of the German Federal Ministry of Environment, Nuclear Safety, and Nature Protection; the Ministry of Environment and Traffic of the state of Baden- Württemberg; the Ministry of Environment of the state of North Rhine-Westphalia; and the MAIFOR Programme of the University of Mainz.

The Japanese Interphone study was fully funded by the Ministry of Internal Affairs and Communications of Japan.

Funding in New Zealand for this project was provided by the Health Research Council of New Zealand, the Cancer Society of New Zealand, the Wellington Medical Research Foundation, the Hawke's Bay Medical Research Foundation and the Waikato Medical Research Foundation.

The Swedish centre was additionally supported by the Swedish Research Council and the Swedish Cancer Society.

The UK North study received additional funding from the Health and Safety Executive, the Department of Health, the Mobile Telecommunications, Health and Research (MTHR) program, and the Scottish Executive. The University of Leeds received some financial support on behalf of the 4 centres of the 'UK North Study' from the UK Network Operators (O2, Orange, T-Mobile, Vodafone, '3') under legal signed contractual agreements which guaranteed complete independence for the scientific investigators.

The Southeast England Centre wishes to acknowledge additional funding from the Mobile Telecommunications, Health and Research (MTHR) programme.

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.

Acknowledgments

The authors like to thank Mr Klaus Schlaefer (German INTERPHONE team) for his contribution to this work and to INTERPHONE Germany in general, who sadly passed away before the end of this project.

The authors are grateful to Lesley Richardson (Montreal, Canada – formerly at IARC) for her major role in the coordination of the study; Emilie Combalot and Helene Tardy for their skillful data management at the coordination centre; Dr Baruch Modan (Israel – deceased) for his assistance and enthusiasm in the design and setting up of this study; James Doughty (UK North), who performed miracles implementing the CAPI in several languages and several

versions, assisted by Roger Parslow (UK North); Jan Ivar Martinsen for additional programming work; Liz Findlay (UK North) who contributed a great deal to the development of materials and training of interviewers; the research assistants and interviewers in the different study centres who ensured that the study was carried out with care and consideration for the participants; the clinical practitioners, particularly neurosurgeons and ear, nose and throat surgeons, who permitted and facilitated our approaches to their patients; and the participants who gave so generously of their time. The Australian team would like to acknowledge the overall support given to study design and implementation by Associate Prof. Michael Besser and Prof. Andrew Kaye; the special support Associate Prof. Besser and Dr Paul Fagan gave to this study of acoustic neuroma. We thank also our fieldwork staff in Melbourne – Monique Kilkenny, Georgina Marr, Tracey McPhail, Fiona Phillips, Hayley Shaw, Yvonne Torn-Broers; and Sydney – Matthew Carroll, Sally Dunlop, Virginia MacDonald and Elizabeth Willows – and the many interviewers for their hard work, and the NSW and Victorian Cancer Registries for aiding case identification. The Canada – Montreal team acknowledges the diligent work of fieldwork staff including Marie-Claire Goulet, Sylvie Plante, Sally Campbell and the interviewer team. The following hospitals and physicians in Montreal permitted access to their patients: CHUM – Hôpital Notre-Dame (Dr Wieslaw Michel Bojanowski, Dr Jean Jacques Dufour, Dr François Lavigne, Dr Robert A. Moumdjian); Neurological Institute of Montreal (Dr Rolando Del Maestro, Dr Richard Leblanc); Hôpital du Sacré -Coeur de Montréal (Dr Marc F. Giroux); The Jewish General Hospital (Dr Gerard Mohr, Dr Jamie Miles Rappaport). The Canada – Ottawa centre gratefully acknowledges the work of the interview team, particularly Lynn Pratt and Daniel Bedard for their leading roles in study coordination; participating clinicians at the Ottawa Hospital included Drs. Brien Benoit, Martin J. Corsten, André Lamothe, William Miller, Paul F. Odell, and David Schramm. The Danish Interphone team likes to thank Michael Kosteljanetz (Neurosurgical Department, Neuroscience Centre, University Hospital of Copenhagen), Hans Skovgaard Poulsen (Department of Radiation Biology, Finsen Centre, University Hospital of Copenhagen) and Jens Thomsen (Department of Otolaryngology– Head and Neck Surgery, Gentofte Hospital, University of Copenhagen, Hellerup). Furthermore, we like to thank Lars H. Thomassen for skilful computer assistance. The Finnish Interphone team acknowledges the roles of Tiina Salminen ja Anna Lahkola in study coordination and research nurse Anu Outinen (STUK), neuropathologist Hannu Haapasalo MD, PhD (Tampere University Hospital, Dept of Pathology), chief physician Risto Sankila, MD, PhD (Finnish Cancer Registry), Prof. Juha Jääskeläinen (Helsinki University Hospital, Dept of Neurosurgery, currently Kuopio University Hospital), Prof. Matti Vapalahti (Kuopio University Hospital, Dept of Neurosurgery), Prof. John Koivukangas (Oulu University Hospital, Dept of Neurosurgery), chief physician Simo Valtanen (Turku University Hospital, Dept of Neurosurgery), chief physician Timo Kuurne (Tampere University Hospital, Dept of Neurosurgery) in collection of the data. The French Interphone team would like to thank the

French fieldwork team: Mary-Pierre Herrscher, Fatima Lamri, Agnès Boidart, H  l  ne Gire, Juliette Krassilchik, Judith Lenti, Delphine Maillac, Fr  d  rique Sonnet, Flore Taguiev, Julie Frantz, France Castay, Florian Gay, for their excellent work; all the hospital services who assisted us in the ascertainment of cases: Lyon – Centre Hospitalier Lyon – Sud (Prof. Dubreuil), H  pital Neurologique Pierre Wertheimer (Prof. Fisher, Prof. Vall  e, Prof. Bret, Prof. Sindou, Prof. Deruty); Paris – H  pital Foch (Prof. Chabolle), H  pital Beaujon (Prof. Sterkers, Dr Bouccara), H  pital Lariboisi  re (Prof. Tran Ba Huy), Marseille – H  pital de la Timone (Prof. Peragut, Dr Regis), as well as all those in the departments of medical information and all the hospital personnel, particularly the secretaries and the staff in the medical archives, whose assistance proved essential to the success of the project. The German Interphone Group would like to thank Stephanie Estel, Marianne Br  mmel, Melanie Kaiser and Anna Wilms for organizing the field phase and all our interviewers for their skilful work. We thank the clinical Interphone team for their support and collaboration (Bielefeld: Prof. Falk Oppel (Neurosurgical Clinic), Dr Uwe Dietrich (Neuroradiology), Dr Volkmar Hans (Neuropathology); Heidelberg: Prof. Andreas Unterberg, Prof. Stefan Kunze, Prof. Dr Karsten Geletneky (Neurosurgical Clinic), Prof. Klaus Sator, Dr Jochen Fiebach (Neuroradiology), Prof. Marika Kiessling (deceased) (Neuropathology); Mannheim: Prof. Peter Schmiedek (deceased), Dr Jochen T  ttenberg (Neurosurgical Clinic), Prof. Christoph Groden, Dino Podlessek (Neuroradiology), Prof. Uwe Bleyl (deceased), Dr Rainer Grobholz (Neuropathology); Mainz: Prof. Axel Perneczky (deceased), Prof. Nico Hopf, Dr Dorothee Koch (Neurosurgical Clinic), Prof. Wolf Mann, Prof. Nickalaos Marangos (ENT Clinic), Dr Wibke M  ller-Forell (Neuroradiology), Prof. Hans Hilmar G  bel (Neuropathology). The Israeli centre wishes to acknowledge the following neurosurgeons for the help they provided in patients recruitment and ascertainment: Prof. Eli Reichenthal (Soroka University Medical Center), Prof. Moshe Hadani and Dr Roberto Spiegelman (Chaim Sheba Medical Center), the late Prof. George Vaaknin (Tel-Aviv Medical Center), Prof. Zvi Harry Rappaport (Rabin Medical Center), Prof. Felix Umansky (Hadassah Hebrew University Medical Center), and Prof. Moshe Feinsod (Rambam Health Care Campus). We acknowledge the diligent work of the fieldwork and office staff including Etti Aviezer, Tehila Ben-Tal, Meirav Dolev, Yonit Deutch, Tamara Rodkin, Ahuva Zultan and the interviewer team. The Italian Interphone team (including Dr Ivano Iavarone, Prof. Bruno Jandolo, Prof. Paolo Vecchia, Dr Stefano Martini, Dr Emanuela Rastelli, Dr Antonello Vidiri, Dr Rita Basili, Dr Caterina Carnovale Scalzo, Dr Edvina Gali  , Eng. Lucia Ardoino, Eng. Enrica Barbieri, Dr Cristiano Tesi, Massimo Lucibello and Rossella Rossi) wishes to thank all the neurosurgeons, ENT-surgeons, neuroradiologists, pathologists, and health managers contributing to the study: Prof. Umberto Agrillo, Dr Amalia Allocca, Dr Mostaf   Amini, Dr Cinzia Bernardi, Dr M. Bonamini, Dr Loredana Bove, Prof. Luigi Bozzao, Dr Alessandro Bozzao, Dr Mario Braga, Dr Fabrizio Breccia, Dr Velia Bruno, Dr Andrea Brunori, Dr Antonella Buffoni, Prof. Arnaldo Capelli, Prof. Giampaolo Cantore, Prof. Natale

Cantucci, Dr Emanuela Caroli, Prof. Cosimo Cassano, Dr Alessandra Castelnuovo, Dr Costanza Cavuto, Prof. Lucia Cecconi, Dr Franco Cerquetani, Dr Carla Colavecchi, Dr Antonio Comberiat, Dr Valeria D'Alfonso, Dr Giovanni De Angelis, Dr Luca de Campora, Prof. Roberto Delfini, Dr Carlo Della Rocca, Prof. Marco De Vincentiis, Dr Domenica Di Stefano, Prof. Stefano Esposito, Prof. Alfredo Fabiano, Dr Francesco Federico, Prof. Luigi Ferrante, Dr Anna Rita Fetoni, Dr Letizia Feudi, Prof. Roberto Filippo, Prof. Roberto Floris, Prof. Felice Giangaspero, Dr Renato Gigli, Dr Marco Giordano, Prof. Gianfranco Gualdi, Prof. G. Guglielmi, Dr Massimo Iachetti, Prof. Giorgio Iannetti, Dr Maria Rosaria Limiti, Prof. Giulio Maira, Dr Valentina Manciooco, Dr Annunziato Mangiola, Dr Ferdinando Marandino, Dr Luisa Marangoni, Prof. Pasquale Marano, Prof. Maria Enrica Martini Neri, Dr Luciano Mastronardi, Dr Arianna Mattioni, Prof. Maurizio Maurizi, Dr Maria Concetta Mazzeo, Dr Giuseppe Natali, Dr Gaetano Nostro, Prof. Emanuele Occhipinti (deceased), Prof. Antonio Orlacchio, Prof. Augusto Orlandi, Prof. Fabrizio Ottaviani, Dr Salvatore Passafaro, Dr Francesco Saverio Pastore, Dr Laura Pennesi, Dr Claudio Maria Pianura, Prof. Roberto Pisa, Dr Chimene Pistolesi, Prof. Giuseppe Poladas, Dr Siavash Rahimi, Prof. Antonio Ricci, Dr Giovanna Ricci, Dr P. Rigotti, Dr Massimo Rimatori, Dr Rossana Romani, Prof. Giuseppe Santeusano, Dr Sergio Santilli, Dr Marco Scarpinati, Dr Lauro Sciannamea, Prof. Luigi Sinibaldi, Prof. Giuseppe Spriano, Dr Maurizio Giovanni Vigili, Dr Antonello Vidiri, Dr Massimo Volpe. We are grateful to Dr Francesco Forastiere, Daniela D'Ippoliti and Stefania Palange (Epidemiologic Unit ASLRME) for their support in case ascertainment from secondary sources and control selection. We acknowledge the collaboration of the Italian mobile phone network operators in providing us with traffic data for the exposure validation studies. The Japanese Interphone team would like to thank Prof. Suminori Akiba (Kahoshima University), Dr Yuriko Kikuchi (Keio University), Prof. Masao Taki (Tokyo Metropolitan University), Drs. Soichi Watanabe and Kanako Wake (National Institute of Information and Communication Technology) for their contributions in planning and conducting the Interphone study in Japan. The Interphone team from New Zealand would like to acknowledge the assistance and support of the neurosurgeons and support staff at the neurosurgical units at Auckland Hospital (headed by Mr Edward Mee), Wellington Hospital (headed by Mr Martin Hunn) and Christchurch Hospital (headed by Mr Martin MacFarlane); the staff at the medical record departments at Auckland Hospital, Wellington Hospital and Christchurch Hospital; the staff at the New Zealand Health Information Service and the New Zealand Cancer Registry; Mr Martin Gledhill at the National Radiation Laboratory; the regional coordinators for the study, Ms Cara Marshall, Ms Sue Hawkins and Ms Janfrey Doak. The Norwegian Interphone team thanks the Cancer Registry of Norway, the hospital staff; especially Prof. Tryggve Lundar (Rikshospitalet University Hospital), Prof. Knut Wester (Haukeland University Hospital), Prof. Bjørn Magnæs (Ullevaal University Hospital) and Dr Johan Cappelen (St. Olav University Hospital). We also thank the interviewers especially Margareth Kaurin for the hard work and dedication. The Swedish Interphone centre thanks the

Swedish Regional Cancer Registries and the hospital staff; especially the following key persons at the hospitals: Dr J. Boethius, Dr O. Flodmark, Prof. I. Langmoen, Dr A. Lilja, Dr T. Mathiesen, Dr I. Olsson Lindblom and Dr H. Stibler (Karolinska University Hospital), Dr J. Lycke, Dr A. Michanek and Prof. L. Pellettieri (Sahlgrenska University Hospital), Prof. T. Möller and Prof. L. Salford (Lund University Hospital). All the interviewers and study administrators from the UK North are thanked for their hard work and dedication. The UK North centre wishes to acknowledge the support of the following neuropathologists, neuroradiologists, neurosurgeons, neuro-oncologists, clinical oncologists, neurologists, specialist nurses and administrators based in hospitals located in Scotland (Mr Barlow, Prof. I. Bone, Ms J. Brown, Mr J. Crowther, Miss R. Dolan, Mr Dunn, Mr M.O. Fitzpatrick, Mrs M. Fraser, Dr R. Grant, Dr A. Gregor, Mr Johnstone, Mr Lyndsay, Mrs S. Macnamara, Miss J. Mair, Mr R. Mills, Miss Myles, Mr B. O'Reilly, Mr V. Papanastassiou, Prof. R. Rampling, Mr Russell, Mr D. Sim, Mr P. Statham, Mr Steers, Mr Taylor, Prof Teasdale, Prof. I. Whittle), west Midlands (Dr J.M. Anderson, Dr Barbour, Dr C.R. Barraclough, Dr P. Bennett, Dr H.G. Boddie, Mr Brind, Dr Carey, Mr M. Choksey, Mr M. Christie, Dr R.N. Corston, Prof. G.S. Cruickshank, Dr A. Detta, Mr P. Dias, Dr S.J. Ellis, Mr G. Flint, Dr D.A. Francis, Mr A.H. Grubneac, Mr S.P. Harland, Dr C. Hawkins, Dr T. Heafield, Dr R.C. Hughes, Dr D.G. Jamieson, Dr A. Logan, Mr C.H.A. Meyer, Mrs R. Mitchell, Prof. K. Morrison, Dr P. Newman, Dr D. Nicholl, Dr S. Nightingale, Dr H.S. Pall, Mr J.R. Ponsford, Dr A. Shehu, Mr Singh, Dr J.A. Spillane, Mr P. Stanworth, Dr B. Summers, Mr A.R. Walsh, Mr J. Wasserberg, Prof. A.C. Williams, Dr J. Winer, Mr S. Zygmunt), Trent (Dr R.J. Abbott, Ms Sheila Adams, Mr Ashpole, Mr R.D.E. Battersby, Prof. L. Blumhardt, Mr P. Byrne, Miss M. Cartmil, Dr S.C. Coley, Dr P. Critchley, Dr Faraj, Dr A. Gibson, Dr P. Griffiths, Dr R. Grunwald, Dr T.J. Hodgson, Mr D.T. Hope, Dr S. Howell, Dr D. Jefferson, Mr D. Jellinek, Dr N. Jordan, Mr A. Kemeny, Dr M.C. Lawden, Prof. J. Lowe, Dr N. Messios, Ms Kirsty Pardoe, Dr S. Price, Dr I.F. Pye, Mr M. Radatz, Mr I. Robson, Dr K. Robinson, Dr C. Romanowski, Dr G. Sawle, Dr B. Sharrock, Prof. P. Shaw, Dr C. Smith, Dr W. Temperley, Dr G. Venables, Mr B. White, Mr A.M. Whiteley, Dr Wills) and West Yorkshire (Dr Al-Din, Dr D. Ash, Dr J. Bamford, Dr M. Bond, Dr G. Bonsor, Dr L. Bridges, Dr B. Carey, Dr Chakrabarty, Mr P. Chumas, Dr D. Dafalla, Dr H. Ford, Dr Gerrard, Dr Goulding, Dr J. Howe, Dr S. Jamieson, Dr Johnson, Dr Louizou, Mr P. Marks, Dr M. Nelson, Dr S. Omer, Mr N. Phillips, Mr S. Ross, Dr I. Rothwell, Dr H. Spokes, Dr J. Straiton, Mr G. Towns, Mr A. Tyagi, Mr P. Vanhille, Dr M. Busby). The Southeast England centre thank the study participants, D. Hogben, A. Butlin, J. Owens, A. Hart, R. Knight, C. Parsley, M. Pelerin, K. Sampson, M. Snigorska and M. Swanwick for help in data collection, Prof. H. Møller, Mr B. Plewa and Mr S. Richards, from the Thames Cancer Registry, and the following consultants and their teams for their support: Mr G. Brookes, Mr A.D. Cheesman, Prof. M.J. Gleeson and Mr N.D. Kitchen (National Hospital for Neurology and Neurosurgery), Mr R. Bradford (Royal Free Hospital), Prof. M. Brada (Royal Marsden Hospital), Mr C. Hardwidge, Mr J.S. Norris and Dr M. Wilkins (Princess Royal Hospital), Mr M.M. Shah,

Prof. A.J. Strong and Mr N. Thomas (King's College Hospital), Prof. A. Bell, Mr H. Marsh and Mr F. Johnston (St George's Hospital), Mr K.S. O'Neill and Mr N.D. Mendoza (Charing Cross Hospital), Mr R. MacFarlane (Addenbrooke's Hospital) and Mr A.R. Aspoas and Mr S. Bavetta (Oldchurch Hospital).

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) (Table 1). 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.

References:

1. Schlehofer B, Siegmund B, Linseisen J, et al. Primary brain tumours and specific serum immunoglobulin E: a case-control study nested in the European Prospective Investigation into Cancer and Nutrition cohort. *Allergy* 2011; 66:1434-41. doi: 10.1111/j.1398-9995.2011.02670.x.
2. Ostrom QT, Bauchet L, Davis FG, et al. The epidemiology of glioma in adults : a « state of the science » review. *Neuro-Oncology*, 2014; 16:896-913. <https://doi.org/10.1093/neuonc/nou087>
3. Turner MC, Krewski D, Armstrong BK, et al. Allergy and brain tumors in the INTERPHONE study: pooled results from Australia, Canada, France, Israel, and New Zealand. *Cancer Causes Control* 2013; 24:949-60. doi: 10.1007/s10552-013-0171-7.
4. Vecht CJ, Kerkhof M, Duran-Pena A. Seizure prognosis in Brain Tumors : New Insights and Evidence-Based Management. *The Oncologist*. 2014; 19:751-759. <http://dx.doi.org/10.1634/theoncologist.2014-0060>
5. Prakash O, Lukiw WJ, Peruzzi F, et al. Gliomas and seizures. *Medical Hypotheses*. 2012; 79:622-626.
6. The Interphone Study Group. Brain tumour risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. *Int J Epidemiol*. 2010. 39: 675-94.
7. The INTERPHONE Study Group. Acoustic neuroma risk in relation to mobile telephone use: Results of the INTERPHONE international case-control study. *Cancer Epidemiol* 2011. 35:453-64.
8. Zhao H, Cai W, Su S et al. Allergic conditions reduce the risk of glioma: a meta-analysis based on 128,936 subjects. *Tumor Biol*. 2014. 35:3875-3880. <https://10.1007/s13277-013-1514-4>.
9. Ostrom QT, Fahmideh MA, Cote DJ, et al. Risk factors for childhood and adult primary brain tumors. *Neuro-Oncology*. 2019. 21:1357-1375. <https://doi.org/10.1093/neuonc/noz123>.
10. Buckingham SC, Robel S. Glutamate and tumor-associated epilepsy: Glial cell dysfunction in the peritumoral environment. *Neurochem.Int*. 2013. [63:696-701](https://doi.org/10.1016/j.neuint.2013.01.027).
<https://dx.doi.org/10.1016/neuint.2013.01.027>

Table 1: Association between tumour and allergy or epilepsy, by time since start¹ and age at onset²

	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)

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

²Reference 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 gender¹

	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)

¹Reference 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
<i>Refused</i>	470	31	339	49	148	62	4303	64
<i>doctor refusal</i>	198	13	69	10	23	10	126	2
<i>dead or too ill</i>	637	42	66	10	5	2	49	1
<i>language problems</i>	34	2	50	7	12	5	133	2
<i>unable to trace</i>	157	10	137	20	46	19	1819	27
<i>other reasons</i>	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

[Click here to view linked References](#)

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

Brigitte Schlehöfer¹, Maria Blettner², Monika Moissonnier³, Isabelle Deltour³, Graham G Giles^{4,5,6}, Bruce Armstrong, Jack Siemiatycki⁸, Marie-Elise Parent⁹, Daniel Krewski¹⁰, Christoffer Johansen¹¹, Anssi Auvinen^{12,13}, Anna Lahkola¹³, Martine Hours¹⁴, Gabriele Berg-Beckhoff¹⁵, Siegal Sadetzki^{16,17,18}, Susanna Lagorio¹⁹, Toru Takebayashi²⁰, Naohito Yamaguchi²¹, Alistair Woodward²², Angus Cook²³, Tore Tynes²⁴, Lars Klaboe²⁵, Maria Feychting²⁶, Richard Feltbower²⁷, Anthony Swerdlow²⁸, Minouk Schoemaker²⁸, Elisabeth Cardis^{29,30,31}, Joachim Schüz³

¹ [private: Leimen, Germany; retired, former: Unit of Environmental Epidemiology](#), German Cancer Research Center (DKFZ), Heidelberg, Germany

² Institute of Medical Biostatistics, Epidemiology and Informatics, University of Mainz, Germany

³ International Agency for Research on Cancer (IARC/WHO), Environment and Lifestyle Epidemiology Branch, Lyon, France

⁴ Cancer Epidemiology Division, Cancer Council Victoria, Melbourne, Victoria, Australia

⁵ Centre for Epidemiology and Biostatistics, School of Population and Global Health, University of Melbourne, Parkville, Victoria, Australia

⁶ Precision Medicine, School of Clinical Sciences at Monash Health, Monash University, Clayton, Victoria, Australia

⁷ School of Public Health, University of Sydney, Sydney, Australia

⁸ University of Montreal, Montreal, Canada

⁹ Institut national de la recherche scientifique (INRS), Laval, Canada

¹⁰ McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, Ottawa, Canada

¹¹ Center for Surgery and Cancer, Rigshospitalet, Copenhagen, Denmark

¹² Tampere University, Faculty of Social Sciences, Finland

¹³ STUK Radiation and Nuclear Safety Authority, Environmental Radiation Surveillance, Helsinki, Finland

¹⁴ Université Lyon 1, IFSTTAR, UMRESTTE, Bron, France

¹⁵ Unit for Health Promotion Research, Department of Public Health, and Hospital South West Jutland Esbjerg; University of Southern Denmark, Denmark

- ¹⁶ Cancer & Radiation Epidemiology Unit, Gertner Institute for Epidemiology & Health Policy Research, Sheba Medical Center, Tel-Hashomer, Israel
- ¹⁷ Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
- ¹⁸ Ministry of Health, Jerusalem, Israel
- ¹⁹ Department of Oncology and Molecular Medicine, Istituto Superiore di Sanità, Rome, Italy
- ²⁰ Department of Preventive Medicine and Public Health, Keio University School of Medicine, Tokyo, Japan
- ²¹ Department of Public Health, Tokyo Women's Medical University School of Medicine, Tokyo, Japan
- ²² School of Population Health, University of Auckland, Auckland, New Zealand
- ²³ Population and Global Health, The University of Western Australia, Perth, WA, Australia
- ²⁴ National Institute of Occupational Health, Oslo, Norway
- ²⁵ Norwegian Radiation Protection Authority, Østerås; The Cancer Registry of Norway, Oslo, Norway
- ²⁶ Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
- ²⁷ School of Medicine, University of Leeds, UK
- ²⁸ Institute of Cancer Research, Sutton, UK
- ²⁹ Barcelona Institute of Global Health (ISGlobal), Barcelona, Spain
- ³⁰ University Pompeu Fabra, Barcelona, Spain
- ³¹ CIBER Epidemiologia y Salud Pública, Madrid, Spain

ORCID-ID

Joachim Schüz <http://orcid.org/0000-0001-9687-2134>
Jack Siemiatycki <https://orcid.org/0000-0002-9042-8582>
Maria Feychting <https://orcid.org/0000-0002-5101-0060>
Susanna Lagorio <https://orcid.org/0000-00001-8883-8745>
Elisabeth Cardis <https://orcid.org/0000-0003-0999-6839>
Gabriele Berg-Beckhoff <https://orcid.org/0000-0003-1614-938X>
Isabelle Deltour <https://orcid.org/0000-0002-6602-6292>
Marie-Elise Parent <https://orcid.org/0000-0002-4196-3773>
Graham Giles <https://orcid.org/0000000349469099>
Anssi Auvinen <https://orcid.org/0000-0003-1125-4818>

Corresponding author: Joachim Schüz, schuzj@iarc.fr

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

Funding:

There was no particular grant for the present work with the core writing group contributing from their regular positions (BS, MB, MM, JS), with some funding for travel and meetings provided by the International Agency for Research on Cancer (IARC/WHO).

The INTERPHONE study was supported by funding from the European Fifth Framework Program, 'Quality of Life and Management of Living Resources' (contract QLK4-CT-1999901563) and the International Union against Cancer (UICC). The UICC received funds for this purpose from the Mobile Manufacturers' Forum and GSM Association. Provision of funds to the INTERPHONE study investigators via the UICC was governed by agreements that guaranteed INTERPHONE's complete scientific independence. The terms of these agreements are publicly available at <https://interphone.iarc.fr/funding>

The Australian centre was supported by the Australian National Health and Medical Research Council (EME Grant 219129) with funds originally derived from mobile phone service licence fees. Cancer Council NSW and Cancer Council Victoria provided most of the infrastructure for the project in Australia.

The Canada – Montreal study was primarily funded by a grant from the Canadian Institutes of Health Research (project 15 MOP-42525). Additionally, Dr Siemiatycki's research team was partly funded by the Canada Research Chair programme and by the Guzzo-CRS Chair in Environment and Cancer. Dr Parent had a salary award from the Fonds de la recherche en santé du Québec.

The Canadian centres in Ottawa/Vancouver were supported by a university–industry partnership grant from the Canadian Institutes of Health Research (CIHR), the latter including partial support from the Canadian Wireless Telecommunications Association. The CIHR university–industry partnerships program also includes provisions that ensure complete scientific independence of the investigators. D. Krewski is the Natural Sciences and Engineering Research Council of Canada Chair in Risk Science at the University of Ottawa.

Additional funding for the study in France was provided by l'Association pour la Recherche sur le Cancer (ARC) [Contrat No. 5142] and three network operators (Orange, SFR, Bouygues Télécom). The funds provided by the operators represented 5% of the total cost of the French study and were governed by contracts guaranteeing the complete scientific independence of the investigators.

The Finnish Interphone study received additional national funding from Emil Aaltonen Foundation and Academy of Finland (Grant No. 80921).

The German Interphone study received additional national funding from the "Deutsches Mobilfunkforschungsprogramm [German Mobile Phone Research Program]" of the German Federal Ministry of Environment, Nuclear Safety, and Nature Protection; the Ministry of Environment and Traffic of the state of Baden- Württemberg; the Ministry of Environment of the state of North Rhine-Westphalia; and the MAIFOR Programme of the University of Mainz.

The Japanese Interphone study was fully funded by the Ministry of Internal Affairs and Communications of Japan.

Funding in New Zealand for this project was provided by the Health Research Council of New Zealand, the Cancer Society of New Zealand, the Wellington Medical Research Foundation, the Hawke's Bay Medical Research Foundation and the Waikato Medical Research Foundation.

The Swedish centre was additionally supported by the Swedish Research Council and the Swedish Cancer Society.

The UK North study received additional funding from the Health and Safety Executive, the Department of Health, the Mobile Telecommunications, Health and Research (MTHR) program, and the Scottish Executive. The University of Leeds received some financial support on behalf of the 4 centres of the 'UK North Study' from the UK Network Operators (O2, Orange, T-Mobile, Vodafone, '3') under legal signed contractual agreements which guaranteed complete independence for the scientific investigators.

The Southeast England Centre wishes to acknowledge additional funding from the Mobile Telecommunications, Health and Research (MTHR) programme.

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.

Acknowledgments

The authors like to thank Mr Klaus Schlaefer (German INTERPHONE team) for his contribution to this work and to INTERPHONE Germany in general, who sadly passed away before the end of this project.

The authors are grateful to Lesley Richardson (Montreal, Canada – formerly at IARC) for her major role in the coordination of the study; Emilie Combalot and Helene Tardy for their skillful data management at the coordination centre; Dr Baruch Modan (Israel – deceased) for his assistance and enthusiasm in the design and setting up of this study; James Doughty (UK North), who performed miracles implementing the CAPI in several languages and several

versions, assisted by Roger Parslow (UK North); Jan Ivar Martinsen for additional programming work; Liz Findlay (UK North) who contributed a great deal to the development of materials and training of interviewers; the research assistants and interviewers in the different study centres who ensured that the study was carried out with care and consideration for the participants; the clinical practitioners, particularly neurosurgeons and ear, nose and throat surgeons, who permitted and facilitated our approaches to their patients; and the participants who gave so generously of their time. The Australian team would like to acknowledge the overall support given to study design and implementation by Associate Prof. Michael Besser and Prof. Andrew Kaye; the special support Associate Prof. Besser and Dr Paul Fagan gave to this study of acoustic neuroma. We thank also our fieldwork staff in Melbourne – Monique Kilkenny, Georgina Marr, Tracey McPhail, Fiona Phillips, Hayley Shaw, Yvonne Torn-Broers; and Sydney – Matthew Carroll, Sally Dunlop, Virginia MacDonald and Elizabeth Willows – and the many interviewers for their hard work, and the NSW and Victorian Cancer Registries for aiding case identification. The Canada – Montreal team acknowledges the diligent work of fieldwork staff including Marie-Claire Goulet, Sylvie Plante, Sally Campbell and the interviewer team. The following hospitals and physicians in Montreal permitted access to their patients: CHUM – Hôpital Notre-Dame (Dr Wieslaw Michel Bojanowski, Dr Jean Jacques Dufour, Dr François Lavigne, Dr Robert A. Moumdjian); Neurological Institute of Montreal (Dr Rolando Del Maestro, Dr Richard Leblanc); Hôpital du Sacré -Coeur de Montréal (Dr Marc F. Giroux); The Jewish General Hospital (Dr Gerard Mohr, Dr Jamie Miles Rappaport). The Canada – Ottawa centre gratefully acknowledges the work of the interview team, particularly Lynn Pratt and Daniel Bedard for their leading roles in study coordination; participating clinicians at the Ottawa Hospital included Drs. Brien Benoit, Martin J. Corsten, André Lamothe, William Miller, Paul F. Odell, and David Schramm. The Danish Interphone team likes to thank Michael Kosteljanetz (Neurosurgical Department, Neuroscience Centre, University Hospital of Copenhagen), Hans Skovgaard Poulsen (Department of Radiation Biology, Finsen Centre, University Hospital of Copenhagen) and Jens Thomsen (Department of Otolaryngology– Head and Neck Surgery, Gentofte Hospital, University of Copenhagen, Hellerup). Furthermore, we like to thank Lars H. Thomassen for skilful computer assistance. The Finnish Interphone team acknowledges the roles of Tiina Salminen ja Anna Lakhola in study coordination and research nurse Anu Outinen (STUK), neuropathologist Hannu Haapasalo MD, PhD (Tampere University Hospital, Dept of Pathology), chief physician Risto Sankila, MD, PhD (Finnish Cancer Registry), Prof. Juha Jääskeläinen (Helsinki University Hospital, Dept of Neurosurgery, currently Kuopio University Hospital), Prof. Matti Vapalahti (Kuopio University Hospital, Dept of Neurosurgery), Prof. John Koivukangas (Oulu University Hospital, Dept of Neurosurgery), chief physician Simo Valtanen (Turku University Hospital, Dept of Neurosurgery), chief physician Timo Kuurne (Tampere University Hospital, Dept of Neurosurgery) in collection of the data. The French Interphone team would like to thank the

French fieldwork team: Mary-Pierre Herrscher, Fatima Lamri, Agnès Boidart, Hélène Gire, Juliette Krassilchik, Judith Lenti, Delphine Maillac, Frédérique Sonnet, Flore Taguiev, Julie Frantz, France Castay, Florian Gay, for their excellent work; all the hospital services who assisted us in the ascertainment of cases: Lyon – Centre Hospitalier Lyon – Sud (Prof. Dubreuil), Hôpital Neurologique Pierre Wertheimer (Prof. Fisher, Prof. Vallée, Prof. Bret, Prof. Sindou, Prof. Deruty); Paris – Hôpital Foch (Prof. Chabolle), Hôpital Beaujon (Prof. Sterkers, Dr Bouccara), Hôpital Lariboisière (Prof. Tran Ba Huy), Marseille – Hôpital de la Timone (Prof. Peragut, Dr Regis), as well as all those in the departments of medical information and all the hospital personnel, particularly the secretaries and the staff in the medical archives, whose assistance proved essential to the success of the project. The German Interphone Group would like to thank Stephanie Estel, Marianne Brömmel, Melanie Kaiser and Anna Wilms for organizing the field phase and all our interviewers for their skilful work. We thank the clinical Interphone team for their support and collaboration (Bielefeld: Prof. Falk Opper (Neurosurgical Clinic), Dr Uwe Dietrich (Neuroradiology), Dr Volkmar Hans (Neuropathology); Heidelberg: Prof. Andreas Unterberg, Prof. Stefan Kunze, [Prof. Dr Karsten Geletneky](#) (Neurosurgical Clinic), Prof. Klaus Sator, Dr Jochen Fiebach (Neuroradiology), Prof. Marika Kiessling ([deceased](#)) (Neuropathology); Mannheim: Prof. Peter Schmiedek ([deceased](#)), Dr Jochen Tüttenberg (Neurosurgical Clinic), Prof. Christoph Groden, Dino Podlessek (Neuroradiology), Prof. Uwe Bleyl ([deceased](#)), Dr Rainer Grobholz (Neuropathology); Mainz: Prof. Axel Perneczky (deceased), Prof. Nico Hopf, Dr Dorothee Koch (Neurosurgical Clinic), Prof. Wolf Mann, Prof. Nickalaos Marangos (ENT Clinic), Dr Wibke Müller-Forell (Neuroradiology), Prof. Hans Hilmar Göbel (Neuropathology). The Israeli centre wishes to acknowledge the following neurosurgeons for the help they provided in patients recruitment and ascertainment: Prof. Eli Reichenthal (Soroka University Medical Center), Prof. Moshe Hadani and Dr Roberto Spiegelman (Chaim Sheba Medical Center), the late Prof. George Vaaknin (Tel-Aviv Medical Center), Prof. Zvi Harry Rappaport (Rabin Medical Center), Prof. Felix Umansky (Hadassah Hebrew University Medical Center), and Prof. Moshe Feinsod (Rambam Health Care Campus). We acknowledge the diligent work of the fieldwork and office staff including Etti Aviezer, Tehila Ben-Tal, Meirav Dolev, Yonit Deutch, Tamara Rodkin, Ahuva Zultan and the interviewer team. The Italian Interphone team (including Dr Ivano Iavarone, Prof. Bruno Jandolo, Prof. Paolo Vecchia, Dr Stefano Martini, Dr Emanuela Rastelli, Dr Antonello Vidiri, Dr Rita Basili, Dr Caterina Carnovale Scalzo, Dr Edvina Galiè, Eng. Lucia Ardoino, Eng. Enrica Barbieri, Dr Cristiano Tesei, Massimo Lucibello and Rossella Rossi) wishes to thank all the neurosurgeons, ENT-surgeons, neuroradiologists, pathologists, and health managers contributing to the study: Prof. Umberto Agrillo, Dr Amalia Allocca, Dr Mostafà Amini, Dr Cinzia Bernardi, Dr M. Bonamini, Dr Loredana Bove, Prof. Luigi Bozzao, Dr Alessandro Bozzao, Dr Mario Braga, Dr Fabrizio Breccia, Dr Velia Bruno, Dr Andrea Brunori, Dr Antonella Buffoni, Prof. Arnaldo Capelli, Prof. Giampaolo Cantore, Prof. Natale

Cantucci, Dr Emanuela Caroli, Prof. Cosimo Cassano, Dr Alessandra Castelnuovo, Dr Costanza Cavuto, Prof. Lucia Cecconi, Dr Franco Cerquetani, Dr Carla Colavecchi, Dr Antonio Comberati, Dr Valeria D'Alfonso, Dr Giovanni De Angelis, Dr Luca de Campora, Prof. Roberto Delfini, Dr Carlo Della Rocca, Prof. Marco De Vincentiis, Dr Domenica Di Stefano, Prof. Stefano Esposito, Prof. Alfredo Fabiano, Dr Francesco Federico, Prof. Luigi Ferrante, Dr Anna Rita Fetoni, Dr Letizia Feudi, Prof. Roberto Filippo, Prof. Roberto Floris, Prof. Felice Giangaspero, Dr Renato Gigli, Dr Marco Giordano, Prof. Gianfranco Gualdi, Prof. G. Guglielmi, Dr Massimo Iachetti, Prof. Giorgio Iannetti, Dr Maria Rosaria Limiti, Prof. Giulio Maira, Dr Valentina Manciooco, Dr Annunziato Mangiola, Dr Ferdinando Marandino, Dr Luisa Marangoni, Prof. Pasquale Marano, Prof. Maria Enrica Martini Neri, Dr Luciano Mastronardi, Dr Arianna Mattioni, Prof. Maurizio Maurizi, Dr Maria Concetta Mazzeo, Dr Giuseppe Natali, Dr Gaetano Nostro, Prof. Emanuele Occhipinti (deceased), Prof. Antonio Orlacchio, Prof. Augusto Orlandi, Prof. Fabrizio Ottaviani, Dr Salvatore Passafaro, Dr Francesco Saverio Pastore, Dr Laura Pennesi, Dr Claudio Maria Pianura, Prof. Roberto Pisa, Dr Chimene Pistoiesi, Prof. Giuseppe Poladas, Dr Siavash Rahimi, Prof. Antonio Ricci, Dr Giovanna Ricci, Dr P. Rigotti, Dr Massimo Rimatori, Dr Rossana Romani, Prof. Giuseppe Santeusano, Dr Sergio Santilli, Dr Marco Scarpinati, Dr Lauro Sciannamea, Prof. Luigi Sinibaldi, Prof. Giuseppe Spriano, Dr Maurizio Giovanni Vigili, Dr Antonello Vidiri, Dr Massimo Volpe. We are grateful to Dr Francesco Forastiere, Daniela D'Ippoliti and Stefania Palange (Epidemiologic Unit ASLRME) for their support in case ascertainment from secondary sources and control selection. We acknowledge the collaboration of the Italian mobile phone network operators in providing us with traffic data for the exposure validation studies. The Japanese Interphone team would like to thank Prof. Suminori Akiba (Kahoshima University), Dr Yuriko Kikuchi (Keio University), Prof. Masao Taki (Tokyo Metropolitan University), Drs. Soichi Watanabe and Kanako Wake (National Institute of Information and Communication Technology) for their contributions in planning and conducting the Interphone study in Japan. The Interphone team from New Zealand would like to acknowledge the assistance and support of the neurosurgeons and support staff at the neurosurgical units at Auckland Hospital (headed by Mr Edward Mee), Wellington Hospital (headed by Mr Martin Hunn) and Christchurch Hospital (headed by Mr Martin MacFarlane); the staff at the medical record departments at Auckland Hospital, Wellington Hospital and Christchurch Hospital; the staff at the New Zealand Health Information Service and the New Zealand Cancer Registry; Mr Martin Gledhill at the National Radiation Laboratory; the regional coordinators for the study, Ms Cara Marshall, Ms Sue Hawkins and Ms Janfrey Doak. The Norwegian Interphone team thanks the Cancer Registry of Norway, the hospital staff; especially Prof. Trygve Lundar (Rikshospitalet University Hospital), Prof. Knut Wester (Haukeland University Hospital), Prof. Bjørn Magnæs (Ullevaal University Hospital) and Dr Johan Cappelen (St. Olav University Hospital). We also thank the interviewers especially Margareth Kaurin for the hard work and dedication. The Swedish Interphone centre thanks the

Swedish Regional Cancer Registries and the hospital staff; especially the following key persons at the hospitals: Dr J. Boethius, Dr O. Flodmark, Prof. I. Langmoen, Dr A. Lilja, Dr T. Mathiesen, Dr I. Olsson Lindblom and Dr H. Stibler (Karolinska University Hospital), Dr J. Lycke, Dr A. Michanek and Prof. L. Pellettieri (Sahlgrenska University Hospital), Prof. T. Möller and Prof. L. Salford (Lund University Hospital). All the interviewers and study administrators from the UK North are thanked for their hard work and dedication. The UK North centre wishes to acknowledge the support of the following neuropathologists, neuroradiologists, neurosurgeons, neuro-oncologists, clinical oncologists, neurologists, specialist nurses and administrators based in hospitals located in Scotland (Mr Barlow, Prof. I. Bone, Ms J. Brown, Mr J. Crowther, Miss R. Dolan, Mr Dunn, Mr M.O. Fitzpatrick, Mrs M. Fraser, Dr R. Grant, Dr A. Gregor, Mr Johnstone, Mr Lyndsay, Mrs S. Macnamara, Miss J. Mair, Mr R. Mills, Miss Myles, Mr B. O'Reilly, Mr V. Papanastassiou, Prof. R. Rampling, Mr Russell, Mr D. Sim, Mr P. Statham, Mr Steers, Mr Taylor, Prof Teasdale, Prof. I. Whittle), west Midlands (Dr J.M. Anderson, Dr Barbour, Dr C.R. Barraclough, Dr P. Bennett, Dr H.G. Boddie, Mr Brind, Dr Carey, Mr M. Choksey, Mr M. Christie, Dr R.N. Corston, Prof. G.S. Cruickshank, Dr A. Detta, Mr P. Dias, Dr S.J. Ellis, Mr G. Flint, Dr D.A. Francis, Mr A.H. Grubneac, Mr S.P. Harland, Dr C. Hawkins, Dr T. Heafield, Dr R.C. Hughes, Dr D.G. Jamieson, Dr A. Logan, Mr C.H.A. Meyer, Mrs R. Mitchell, Prof. K. Morrison, Dr P. Newman, Dr D. Nicholl, Dr S. Nightingale, Dr H.S. Pall, Mr J.R. Ponsford, Dr A. Shehu, Mr Singh, Dr J.A. Spillane, Mr P. Stanworth, Dr B. Summers, Mr A.R. Walsh, Mr J. Wasserberg, Prof. A.C. Williams, Dr J. Winer, Mr S. Zygmunt), Trent (Dr R.J. Abbott, Ms Sheila Adams, Mr Ashpole, Mr R.D.E. Battersby, Prof. L. Blumhardt, Mr P. Byrne, Miss M. Cartmil, Dr S.C. Coley, Dr P. Critchley, Dr Faraj, Dr A. Gibson, Dr P. Griffiths, Dr R. Grunwald, Dr T.J. Hodgson, Mr D.T. Hope, Dr S. Howell, Dr D. Jefferson, Mr D. Jellinek, Dr N. Jordan, Mr A. Kemeny, Dr M.C. Lawden, Prof. J. Lowe, Dr N. Messios, Ms Kirsty Pardoe, Dr S. Price, Dr I.F. Pye, Mr M. Radatz, Mr I. Robson, Dr K. Robinson, Dr C. Romanowski, Dr G. Sawle, Dr B. Sharrock, Prof. P. Shaw, Dr C. Smith, Dr W. Temperley, Dr G. Venables, Mr B. White, Mr A.M. Whiteley, Dr Wills) and West Yorkshire (Dr Al-Din, Dr D. Ash, Dr J. Bamford, Dr M. Bond, Dr G. Bonsor, Dr L. Bridges, Dr B. Carey, Dr Chakrabarty, Mr P. Chumas, Dr D. Dafalla, Dr H. Ford, Dr Gerrard, Dr Goulding, Dr J. Howe, Dr S. Jamieson, Dr Johnson, Dr Louizou, Mr P. Marks, Dr M. Nelson, Dr S. Omer, Mr N. Phillips, Mr S. Ross, Dr I. Rothwell, Dr H. Spokes, Dr J. Straiton, Mr G. Towns, Mr A. Tyagi, Mr P. Vanhille, Dr M. Busby). The Southeast England centre thank the study participants, D. Hogben, A. Butlin, J. Owens, A. Hart, R. Knight, C. Parsley, M. Pelerin, K. Sampson, M. Snigorska and M. Swanwick for help in data collection, Prof. H. Møller, Mr B. Plewa and Mr S. Richards, from the Thames Cancer Registry, and the following consultants and their teams for their support: Mr G. Brookes, Mr A.D. Cheesman, Prof. M.J. Gleeson and Mr N.D. Kitchen (National Hospital for Neurology and Neurosurgery), Mr R. Bradford (Royal Free Hospital), Prof. M. Brada (Royal Marsden Hospital), Mr C. Hardwidge, Mr J.S. Norris and Dr M. Wilkins (Princess Royal Hospital), Mr M.M. Shah,

Prof. A.J. Strong and Mr N. Thomas (King's College Hospital), Prof. A. Bell, Mr H. Marsh and Mr F. Johnston (St George's Hospital), Mr K.S. O'Neill and Mr N.D. Mendoza (Charing Cross Hospital), Mr R. MacFarlane (Addenbrooke's Hospital) and Mr A.R. Aspoas and Mr S. Bavetta (Oldchurch Hospital).

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) (Table 1). 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.

References:

1. Schlehofer B, Siegmund B, Linseisen J, et al. Primary brain tumours and specific serum immunoglobulin E: a case-control study nested in the European Prospective Investigation into Cancer and Nutrition cohort. *Allergy* 2011; 66:1434-41. doi: 10.1111/j.1398-9995.2011.02670.x.
2. Ostrom QT, Bauchet L, Davis FG, et al. The epidemiology of glioma in adults : a « state of the science » review. *Neuro-Oncology*, 2014; 16:896-913. <https://doi.org/10.1093/neuonc/nou087>
3. Turner MC, Krewski D, Armstrong BK, et al. Allergy and brain tumors in the INTERPHONE study: pooled results from Australia, Canada, France, Israel, and New Zealand. *Cancer Causes Control* 2013; 24:949-60. doi: 10.1007/s10552-013-0171-7.
4. Vecht CJ, Kerkhof M, Duran-Pena A. Seizure prognosis in Brain Tumors : New Insights and Evidence-Based Management. *The Oncologist*. 2014; 19:751-759. <http://dx.doi.org/10.1634/theoncologist.2014-0060>
5. Prakash O, Lukiw WJ, Peruzzi F, et al. Gliomas and seizures. *Medical Hypotheses*. 2012; 79:622-626.
6. The Interphone Study Group. Brain tumour risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. *Int J Epidemiol*. 2010. 39: 675-94.
7. The INTERPHONE Study Group. Acoustic neuroma risk in relation to mobile telephone use: Results of the INTERPHONE international case-control study. *Cancer Epidemiol* 2011. 35:453-64.
8. Zhao H, Cai W, Su S et al. Allergic conditions reduce the risk of glioma: a meta-analysis based on 128,936 subjects. *Tumor Biol*. 2014. 35:3875-3880. <https://10.1007/s13277-013-1514-4>.
9. Ostrom QT, Fahmideh MA, Cote DJ, et al. Risk factors for childhood and adult primary brain tumors. *Neuro-Oncology*. 2019. 21:1357-1375. <https://doi.org/10.1093/neuonc/noz123>.
10. Buckingham SC, Robel S. Glutamate and tumor-associated epilepsy: Glial cell dysfunction in the peritumoral environment. *Neurochem.Int*. 2013. [63:696-701](https://doi.org/10.1016/j.neuint.2013.01.027).
<https://dx.doi.org/10.1016/neuint.2013.01.027>

Table 1: Association between tumour and allergy or epilepsy, by time since start¹ and age at onset²

	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)

Formatted Table

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)

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

²Reference 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 gender¹

	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)

¹Reference 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
<i>refused-self</i>	470	31	339	49	148	62	4303	64
<i>doctor refusal</i>	198	13	69	10	23	10	126	2
<i>dead or too ill</i>	637	42	66	10	5	2	49	1
<i>language problems</i>	34	2	50	7	12	5	133	2
<i>unable to trace</i>	157	10	137	20	46	19	1819	27
<i>other reasons</i>	40	3	29	4	6	3	266	4
Interviewed <i>but excluded</i> 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	51	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												
<u>University</u> /high level technical/ <u>postgraduate</u> <u>postgrad</u>	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

Formatted Table

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 their 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

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:*

<http://www.springer.com/gp/authors-editors/journal-author/journal-author-helpdesk/publishing-ethics/14214>

All authors of papers submitted to European Journal of Epidemiology
[include name of journal] must complete this form and disclose any real or perceived conflict of interest.

Please complete one form per author. The corresponding author collects the conflict of interest disclosure forms from all authors. The corresponding author will include a summary statement that reflects what is recorded in the potential conflict of interest disclosure form(s). Please check the Instructions for Authors where to put the statement which may be different dependent on the type of peer review used for the journal. Please note that you cannot save the form once completed. Please print upon completion, sign, and scan to keep a copy for your files.

The corresponding author should be prepared to send potential conflict of interest disclosure form if requested during peer review or after publication on behalf of all authors (if applicable).

I have no potential conflict of interest.

Category of disclosure	Description of Interest/Arrangement

Article title Association of allergic diseases 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 Date 4 October 2021