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Occupational exposure to high-frequency electromagnetic fields and brain tumor risk in the INTEROCC study: An individualized assessment approach

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ABSTRACT

Introduction: In 2011, the International Agency for Research on Cancer classified radiofrequency (RF) electromagnetic fields (EMF) as possibly carcinogenic to humans (group 2B), although the epidemiological evidence for the association between occupational exposure to RF-EMF and cancer was judged to be inadequate, due in part to limitations in exposure assessment. This study examines the relation between occupational RF and intermediate frequency (IF) EMF exposure and brain tumor (glioma and meningioma) risk in the INTEROCC multinational population-based case-control study (with nearly 4000 cases and over 5000 controls), using a novel exposure assessment approach.

Methods: Individual indices of cumulative exposure to RF and IF-EMF (overall and in specific exposure time windows) were assigned to study participants using a source-exposure matrix and detailed interview data on work with or nearby EMF sources. Conditional logistic regression was used to investigate associations with glioma and meningioma risk.

Results: Overall, around 10% of study participants were exposed to RF while only 1% were exposed to IF-EMF. There was no clear evidence for a positive association between RF or IF-EMF and the brain tumors studied, with most results showing either no association or odds ratios (ORs) below 1.0. The largest adjusted ORs were obtained for cumulative exposure to RF magnetic fields (as A/m-years) in the highest exposed category (≥90th

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percentile) for the most recent exposure time window (1–4 years before the diagnosis or reference date) for both glioma, OR = 1.62 (95% confidence interval (CI): 0.86, 3.01) and meningioma (OR = 1.52, 95% CI: 0.65, 3.55). *Conclusion:* Despite the improved exposure assessment approach used in this study, no clear associations were identified. However, the results obtained for recent exposure to RF electric and magnetic fields are suggestive of a potential role in brain tumor promotion/progression and should be further investigated.

1. Introduction

Glioma and meningioma are the most frequent primary brain tumor types in adults. Gliomas originate in the glial tissue and are mostly malignant, representing around 80% of all malignant brain tumors (Bondy et al., 2008; Schwartzbaum et al., 2006; Wiemels et al., 2010). Meningiomas are commonly benign, although approximately 5% are malignant (Wiemels et al., 2010). The etiologies of these diseases remain largely unknown. The only well-established risk factors, ionizing radiation and genetic disorders, account for a small portion of cases (Bondy et al., 2008; Ostrom et al., 2014). The current evidence for other possible risk factors, such as non-ionizing radiation (mostly for extremely-low frequency and radiofrequency electromagnetic fields) and certain chemicals, is inconclusive (Bondy et al., 2008; Braganza et al., 2012; Quach et al., 2016; SCENIHR, 2015).

High-frequency electromagnetic fields (EMF) are a form of non-ionizing radiation and comprise, as defined in the international INTEROCC study, intermediate frequency (IF) EMF, between 3 kHz and 10 MHz, and radiofrequency (RF) EMF, between 10 MHz and 300 GHz. The International Agency for Research on Cancer (IARC) classified RF-EMF as possibly carcinogenic to humans (group 2B) in 2011, based on *limited animal evidence*, mostly from co-carcinogenicity experiments, and *limited epidemiological evidence*, mainly based on associations between use of cellular telephones and glioma and acoustic neuroma risk (IARC, 2013). The limited evidence from animal experiments was partly based on studies that examined RF-EMF exposure in combination with known carcinogens whose results, recently replicated (Lerchl et al., 2015), suggested that RF-EMF may act in the promotion and/or progression of already initiated tumors.

The biophysical mechanism(s) by which RF-EMF might play a role in brain tumors are not clear. Both thermal effects, caused by the absorption of RF energy at a rate greater than the body's cooling mechanism (ICNIRP, 1998), and non-thermal hypotheses (Barnes and Greenebaum, 2016, 2015; Blackman et al., 1980; Castello et al., 2014; Rao et al., 2008) have been proposed, including oxidative stress, due to the formation of radical pairs, and calcium efflux, due to activation of voltage-gated calcium channels. For IF-EMF, only very limited evidence exists from some available in vivo studies while, to our knowledge, no specific epidemiologic study of IF exposure has been conducted (SCENIHR, 2015; Sienkiewicz et al., 2010).

Epidemiologic evidence on brain tumor risk from occupational exposure to RF-EMF is inadequate and few recent studies have been performed (Armstrong et al., 1994; Baldi et al., 2011; Berg et al., 2006; Degrave et al., 2009; Grayson, 1996; Groves et al., 2002; Karipidis et al., 2007; Lagorio et al., 1997; Lilienfeld et al., 1978; Morgan et al., 2000; Robinette et al., 1980; Szmigielski, 1996; Thomas et al., 1987; Tynes et al., 1996). Exposure assessment in most of these studies was mainly based on exposure surrogates, such as distance to the source or specific job titles or groups of workers thought to be exposed to RF fields, using occupational duties, qualitative exposure estimates assigned by hygienists (Berg et al., 2006) or job-exposure matrices based on expert judgments (Groves et al., 2002; Karipidis et al., 2007; Morgan et al., 2000; Robinette et al., 1980). Only a few studies, involving military personnel (Szmigielski, 1996), radio and telegraph operators (Tynes et al., 1996) or embassy employees (Lilienfeld et al., 1978) used quantitative exposure estimates based on measurements of RF field intensities. However, exposure estimates were generally based on a small number of measurements and changes in exposure levels over time were not considered. Sample sizes in these studies were also small (Smith and Kriebel, 2010).

As part of the INTEROCC study's aim to improve upon the exposure assessments in previous studies, a source-exposure matrix (SEM) was developed (Vila et al., 2017), containing confidence-weighted mean estimates, based mainly on measurements collected from the literature (Vila et al., 2016), for the EMF sources reported by the study participants. In the current paper, we used the SEM, together with detailed information collected through interviews on work with or nearby occupational EMF sources to derive individual indices of cumulative RF and IF exposure. These metrics were used to study the possible association between cumulative occupational exposure to RF or IF-EMF and glioma or meningioma risk, both overall and in specific exposure time windows.

2. Methods

2.1. Study population

The INTEROCC study comprises data from seven of the thirteen countries included in the international case-control study on mobile phone use and brain cancer risk, INTERPHONE (Cardis et al., 2007). In these seven countries, together with the mobile phone-specific data, detailed occupational information was also collected from study participants. Incident cases of primary brain tumors (i.e. glioma and meningioma) were identified between 2000 and 2004 in participating hospitals in the study regions of Australia, Canada, France, Germany, Israel, New Zealand and the United Kingdom. The core INTERPHONE protocol (Cardis et al., 2007) included cases aged 30 to 59 years of age, though several countries included cases from a broader age range, including up to 69 years in Germany, 18 years and above in Israel and 18 to 69 years in the United Kingdom. Controls were randomly selected from population registries and electoral lists in most countries. Patient lists were used in the UK and random digit dialing in Ottawa (Canada). To control for potential confounding and enhance statistical efficiency (Rothman and Greenland, 1998), controls were individually-matched to cases by age (5-year groups), sex, study region and country. Case-control ratios were 1:1 in all countries but Germany (1:2). All potential participants identified were contacted, informed about the study and asked whether they wanted to participate. For subjects who agreed, a signed informed consent was obtained before the interview process.

In total, the INTEROCC study comprises 2054 glioma cases, 1924 meningioma cases, and 5601 controls. Overall participation rates for cases in INTERPHONE were 65% for glioma and 78% for meningioma cases, although numbers varied by tumor type and center. Participation among glioma cases for low- and high-grade tumors was similar (71% and 67%, respectively). The participation rate among controls was lower (53%) than among cases. The most frequent reasons for non-participation were refusal (64%) and inability to contact (27%), including physician refusal to contact (5% of glioma, 2% of meningioma cases). Most participants were interviewed in person and only a few subjects were interviewed by telephone (5% and 6%, for controls and cases respectively). Proxy respondents were allowed (e.g. 13% for glioma cases overall) if the subject had died or was unable to participate. A computer-assisted personal interview (CAPI) system was used during the interviews. Further details of the questionnaire and the interview process can be found elsewhere (Cardis et al., 2007; Vila et al., 2016). Ethics approval was obtained from IARC's Ethics Committee and

appropriate ethics committees in all participating countries for the INTERPHONE study, as well as from the Ethics Committee of the Municipal Institute for Medical Investigation (IMIM) in Barcelona, Spain, for use of the anonymised INTERPHONE and INTEROCC data.

2.2. Data collection

Detailed occupational-specific data were collected in seven of the thirteen INTERPHONE countries, which comprise the INTEROCC data. Study interviews took place between 2000 and 2004 and lifetime occupational history data were collected. A full occupational calendar for all jobs held for at least six months (including job title, start and stop date, and company name and description) was completed. In addition, the occupational questionnaire included screening questions designed to identify subjects with potential high levels of EMF exposure. The screening questions focused on work with or in the proximity of specific EMF sources with frequencies from 0 Hz to 300 GHz. A positive response to any of the screening questions led to more specific questions concerning the job in which this exposure occurred, including the tasks (e.g. broadcasting, heating), materials (e.g. metals, rubber), process schemes (e.g. automation), and other work organization details, as well as start and stop years, and the number of hours per week/month worked with/nearby the EMF sources reported. A detailed description of the screening questions is available elsewhere (Vila et al., 2016).

2.3. Exposure assessment

The source-exposure matrix (SEM) was used to assign average exposure levels to each RF and IF source reported by the study participants. Of the twelve occupational sections in the questionnaire, seven of them entailed work with sources of RF and/or IF-EMF. These sections involved work with or nearby 1) radars, 2) telecommunication antennas, 3) transmitters (e.g. walkie-talkies), or equipment for 4) semiconductors manufacturing, 5) medical diagnosis and treatment (e.g. hyperthermia), 6) industrial heating (e.g. induction furnaces) or 7) food heating (e.g. microwave drying ovens). The remaining five sections entailed exposure to extremely-low frequency (ELF) EMF only and will be considered elsewhere. Extensive details of the twelve occupational sections, including a summary of the questionnaire, have already been published (Vila et al., 2016).

To combine exposures from different-frequency sources within each frequency band (i.e. RF or IF), field intensities for each EMF source in the SEM were weighted using the frequency-dependent reference levels (RLs) issued by the International Commission on Non-Ionizing Radiation Protection (ICNIRP) for occupational exposure (ICNIRP, 1998). For RF sources with different frequency ranges, E- and H-fields were weighted by the corresponding ICNIRP RLs. ICNIRP reference levels for frequencies above 10 MHz are obtained from basic restrictions for Specific Absorption Rate (SAR). Since the potential for biological effects is associated with the power or energy deposition and the squares of electric and magnetic fields are proportional to power (Hitchcock, 2015), we calculated squared ratios for RF E- and H-fields using available data from the SEM. Thus, RF electric and magnetic field squared ratios (Eq. (1)) can be assumed to correlate with SAR, and their cumulative exposure over time correlates with the specific absorbed energy. For IF sources, RLs for frequencies below 10 MHz were obtained from basic restrictions for current density (in mA/m^2) (and SAR above 100 kHz). Therefore, we calculated (linear) ICNIRP ratios obtained from IF H-fields which may be considered proportional to current density (Eq. (2)). Moreover, since the fields emitted by many IF sources tend to be purely magnetic in nature and there is negligible propagating field (ICNIRP, 2004; Joseph et al., 2012), only H-fields were used to assess exposures to IF sources.

$$\text{RF SAR} \propto \text{ICNIRP ratio}^2(E_s) = \overline{E}_s^2(f_s)/E_{RL}^2(f_s)$$
$$\text{RF SAR} \propto \text{ICNIRP ratio}^2(H_s) = \overline{H}_s^2(f_s)/H_{RL}^2(f_s) \quad (1)$$

$$\text{IF current density} \propto \text{ICNIRP ratio}(H_s) = \overline{H}_s(f_s)/H_{RL}(f_s) \quad (2)$$

where $\overline{E}_s$ represent the mean electric field strength (E, in V/m) for the RF source s from the SEM; $\overline{H}_s$ represents the mean magnetic field strength (H, in A/m) for the IF or RF source s from the SEM; E_{RL} and H_{RL} are the ICNIRP's frequency-dependent reference levels for occupational exposure (ICNIRP, 1998); and f is the frequency.

In addition, since internal magnetic fields are proportional to incident magnetic fields and their penetration into the body has little frequency dependence (Barnes and Greenebaum, 2015), to account for potential non-thermal effects we also used (frequency-unweighted) RF H-fields in our analyses as an alternative metric to assess cumulative exposure to RF magnetic fields.

Cumulative exposure (in ICNIRP ratio- or squared ratio-years) was calculated by using the confidence-weighted (arithmetic) mean exposure level of each reported RF or IF source(s) from the SEM. This was adjusted by information on distance to the source, automation and other modifiers depending on the specific occupational section. Finally, the frequency of working with or in the proximity of these sources (in hours per day/week) and the duration (in years) that this exposure took place was used to calculate indices of cumulative exposure. This detailed information was reported by each INTEROCC participant and depends on the type of RF or IF source reported. For example, frequency of exposure to walkie-talkies refers to the number of hours per day/week that the subject used this source to talk with other co-workers. See Appendix 2 for further details of the methods used to assess cumulative exposure of study participants to RF or IF-EMF.

The quality of the data collected on EMF sources and ancillary information was assessed through comparisons with the data in the full occupational histories. Errors identified, such as incongruent dates or responses not obeying the questionnaire logic, were corrected. Imputation of missing data on exposure rate was performed using median values from control participants. Subjects for which imputation or correction of unreliable data was not possible, and participants with insufficient information to assign an exposure estimate (i.e. due to unclear EMF source and/or exposure duration), were excluded from the analysis.

2.4. Statistical analysis

Although the INTERPHONE study generally included one matched control per case, all eligible controls (n = 5378) were used in both the glioma and meningioma analyses to maximize statistical power. The date of diagnosis was the reference date for cases. The reference date for controls was the date of interview minus the median difference between diagnosis and the case interview date by country.

Conditional logistic regression models using strata defined by the matching factors were used to estimate adjusted odds ratios (ORs) and 95% confidence intervals for the association between cumulative exposure to RF E- or H-fields, or IF H-fields and glioma or meningioma risk. All models were stratified by age (5-year groups), sex, study region and country, and adjusted for education (Cardis et al., 2007). Associations with lifetime cumulative exposure (1-year lag), cumulative exposure at 5- and 10-year lags, as well as cumulative exposure in different time windows defined a priori (1–4, and 5–9 years before the reference date) were examined. These time windows were chosen to assess the hypothesis that recent exposures to RF and/or IF-EMF may entail different risks, possibly related to tumor promotion or progression (Smith and Kriebel, 2010; Turner et al., 2014), than exposures further in the past.

Both categorical and continuous indicators of RF and IF-EMF cumulative exposure were examined. Due to skewed distributions of exposure data, irregular cut-points (i.e. 50th, 75th and 90th percentiles) were used to define categories that spanned the range of the exposure

distribution. For IF, due to the smaller number of exposed subjects (1%), the median value (i.e. 50th percentile) among exposed subjects was used as the only cut point. The reference category for the main analysis was subjects never exposed to occupational RF or IF-EMF.

For the continuous analyses, exposure was modelled linearly and departure from linearity was tested using polynomials and logarithmic transformation of exposure. Models adequacy, in terms of goodness of fit, was evaluated using the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) (Röösli and Vienneau, 2014; Vrieze, 2012). The symmetry of the log-likelihood function in each model was assessed to confirm the adequacy of Wald-type confidence intervals (Hosmer et al., 2013). Due to the small number of subjects exposed to IF fields, the continuous analysis was only performed using RF E- and H-fields.

Potential confounding by any allergy history (Turner et al., 2013), mobile phone use (never vs ever regular user) (Cardis et al., 2011) and any medical ionizing radiation (Bondy et al., 2008) was also examined using a 10% change in the risk estimate criterion (Cardis et al., 2007; Mickey and Greenland, 1989). Analyses were also conducted for high- and low-grade glioma types, separately. Potential effect modification by matching variables was assessed by including in the models cross-product terms between exposure and these variables and assessing the significance of the likelihood ratio test between models with and without the interaction term (Hosmer et al., 2013).

Sensitivity analyses were performed by using the lowest exposure category rather than the unexposed group as the reference category, or excluding proxy interviewees, participants who were judged by the interviewers as non-collaborative, participants aged > 60 years, participants with very high (> 99th percentile) or very low (< 1st percentile) cumulative exposure levels, and participants with a history of neurofibromatosis or tuberous sclerosis.

All analyses and graphics were performed using R, version 3.2.3 (R Core Team, 2014). Regression models were created using the "clogit" function (Therneau, 2015).

Table 1
Distribution of included study participants by age, sex, education, country, region and occupational section. INTEROCC study. Data from Australia, Canada, France, Germany, Israel, New Zealand, and United Kingdom, 2000–2004.

Variable		Glioma cases		Controls		Meningioma cases		Controls	
		n	%	*n*	%	*n*	%	*n*	%
		1943	100	5387	100	1862	100	5387	100
Age[a]									
< 35		214	11%	413	8%	82	4%	415	8%
35–39		171	9%	454	8%	97	5%	457	9%
40–44		216	11%	624	12%	166	9%	622	12%
45–49		239	12%	726	14%	269	14%	730	14%
50–54		347	18%	955	18%	370	20%	963	18%
55–59		310	16%	992	18%	319	17%	980	18%
60–64		190	10%	501	9%	189	10%	499	9%
65–69		140	7%	433	8%	170	9%	434	8%
70+		116	6%	289	5%	200	11%	287	5%
Sex									
Male		1162	60%	2350	44%	485	26%	2350	44%
Female		781	40%	3037	56%	1377	74%	3037	56%
Education[b]									
High school or less		1034	53%	2914	54%	1125	60%	2914	54%
Medium-level technical school		376	19%	1004	19%	357	19%	1004	19%
University		533	27%	1469	27%	380	20%	1469	27%
Country	Region								
Australia	Melbourne	135	15%	305	12%	121	13%	305	12%
	Sydney	147		337		120		337	
Canada	Montreal	63	8%	225	12%	47	5%	225	12%
	Ottawa	21		172		14		172	
	Vancouver	78		229		31		229	
France	Paris	28	5%	112	9%	41	8%	112	9%
	Lyon	63		351		103		351	
Germany	Bielefeld	99	18%	438	28%	100	20%	438	28%
	Heidelberg/Mannheim	179		709		206		709	
	Mainz	77		360		70		360	
Israel	–[c]	418	22%	958	18%	722	39%	1611	18%
New Zealand	–[c]	80	4%	158	3%	50	3%	158	3%
United Kingdom	Scotland	139	29%	269	19%	62	13%	269	19%
	West Yorkshire	121		232		60		232	
	West Midlands	105		182		24		182	
	West Trent	190		350		91		350	
Occupational section[d]									
Diagnosis & treatment		12	2%	83	5%	14	4%	83	5%
Food & medical-dental heating		75	12%	268	16%	85	22%	268	16%
Industrial heating		160	26%	441	27%	111	29%	441	27%
Radars		18	3%	81	5%	19	5%	81	5%
Semiconductors		6	1%	17	1%	3	1%	17	1%
Telecommunication antennas		38	6%	61	4%	11	3%	61	4%
Transmitters		299	49%	674	41%	137	36%	674	41%

[a] 5-year age groups as used for the matching of cases and controls in the recruitment.
[b] A total of 16 cases and 11 controls were excluded due to missing information for Education.
[c] No specific regions were considered for these countries.
[d] Subjects not assigned to any section were considered unexposed.

Table 2
RF and IF sources most frequently reported by the INTEROCC study participants and sources reported with the highest levels of exposure. INTEROCC study. Data from Australia, Canada, France, Germany, Israel, New Zealand, and United Kingdom, 2000–2004.

Most frequent sources							Sources with highest mean exposure levels[a]					
Radiofrequency (10 MHz–300 GHz)				Intermediate frequency (3 kHz–10 MHz)			Radiofrequency (10 MHz–300 GHz)				Intermediate frequency (3 kHz–10 MHz)	
Source	E-field (V/m)[a]	H-field (A/m)[a]	N[b]	Source	H-field (A/m)[a]	N[b]	Source	E-field (V/m)[a]	H-field (A/m)[a]	N[b]	Source	H-field (A/m)[a]	N[b]
Walkie-talkie	335	0.20	411	Induction heater/furnace for metals	0.73	56	RF sealers/welders for plastic & rubber	459	0.70	27	Electronic Article Surveillance (EAS)	12.3	3
Microwave heating	23.4	0.11	174	Dielectric heater/plastic & rubber	1.8	28	Walkie-talkie	335	0.20	411	Plasma etcher/metal etcher/dry plasma etcher	4.99	9
Two-way radio/on motorcycle	14	0.09	174	Glue heater curer/wood & fiber glass	0.19	16	TV/VHF/mast/worked on	310	1.4	1	Plasma-enhanced chemical vapor deposition (CVD)	4.99	4
CB radio	202	0.12	153	Surgical diathermy equipment/ surgeon	5.09	12	Continuous short-wave diathermy	299	0.73	12	Electrical resistance furnaces/metals	3.1	32
RF sealers/welders for plastic & rubber	459	0.70	27	Ultrasound diathermy/physiotherapist	0.21	12	Shuttle tray machine for plastic & rubber	264	0.67	2	Dielectric heater/plastic & rubber	1.8	28
Telecomm. and personal services misc./ ground/surrounding	11.1	–	24	Plasma etcher/metal etcher/dry plasma etcher	4.99	9	CB radio	202	0.12	168	Metal detectors	1.27	4
dielectric heater/plastic & rubber	102	0.91	22	Plasma-enhanced chemical vapor deposition (CVD)	0.26	4	TV/UHF/mast/worked on	210	0.28	8	Induction heater/furnace for metals	0.73	56
Navigation radar/work surrounded	1.23	–	20	Induction welding/metal	3.55	4	Microwave diathermy/ physiotherapist	106	0.32	7	Dielectric heater/wood & fiber glass	0.72	1
Mobile phone base station antennas/ ground/worked on	0.36	–	16	Gluing press/wood & fiber glass	0.72	6	dielectric heater/plastic & rubber	102	0.91	28	Gluing press/wood & fiber glass	0.72	6
Pulsed short wave diathermy	60.1	0.23	16	Electronic Article Surveillance (EAS)	12.3	3	Radio/FM/mast/worked on	92	0.22	1	Induction welding/metal	0.72	4

[a] Arithmetic mean exposure levels from the SEM. RF sources organized by E-field exposure level.
[b] *N*: number of subjects who reported work with or nearby the EMF source.

3. Results

In total, 1943 glioma cases, 1862 meningioma cases, and 5387 controls were included in the analysis. A small number of participants were excluded due to insufficient information on exposure intensity (i.e. EMF source(s) not clearly identified) and/or exposure duration (n = 355), or missing data on education (n = 32). Table 1 describes cases and controls included in the analysis. Meningioma cases tended to be slightly older on average than glioma cases, and were mainly (74%) female, compared with only 40% for glioma. The reported sources with the highest exposure levels were "RF sealers/welders for plastic & rubber", for RF, and "Electronic Article Surveillance (EAS) system", for IF (Table 2). The RF and IF sources most frequently reported were "walkie-talkie" and "induction heater", respectively. Tables S3 and S4 list all the RF and IF sources reported by the study participants by occupational section and frequency of reporting. The mean (SD) number of sources per subject was 1.33 (0.83) for glioma cases and 1.31 (0.65) for meningioma cases, and 1.35 (0.92) for controls. Overall, 10% of participants were ever exposed to RF E- or H-fields overall (1-year lag), while only 1% were ever exposed to IF H-fields at work.

Fig. 1 presents the levels of cumulative exposure to RF E- and H-fields of exposed subjects overall (1-year lag) and in the 1–4 years exposure time window. Table S1 of the Supplementary material (Appendix 1) contains detailed descriptive statistics for these metrics. Table S2 and Fig. S1 describe the data for IF cumulative exposure of study participants. Exposure distributions for all fields and exposure lags and time windows were right-skewed. There was generally little difference in exposure distributions between cases and controls. Median exposure levels in the 1–4 years exposure time window were slightly higher among cases for RF $ICNIRP_E^2$ and H-fields for glioma, and $ICNIRP_H^2$ and H-fields for meningioma.

There was no clear evidence for a positive association between cumulative exposure to (frequency-weighted) RF E-fields (Table 3) and H-fields (Table S5) or (frequency-unweighted) RF H-fields (Table 4) and glioma or meningioma risk overall (1-year lag), or in any other exposure lags or time windows, using categorical classifications of cumulative exposure. In all analyses, there were reduced ORs in most exposure categories. There were no statistically significant elevated ORs for glioma or meningioma observed in any of the exposure categories. The largest ORs were obtained in the analysis of glioma and (frequency-unweighted) RF H-fields (A/m-years) in the highest exposed category (> 90th percentile) in the 1–4 years exposure time window, OR = 1.62 (95% CI: 0.86, 3.01, based on 19 exposed cases), while results for (frequency-weighted) RF E-fields ($ICNIRP_E$ ratio^2-years) and H-fields ($ICNIRP_H$ ratio^2-years) and the same exposure category and time window were slightly lower, OR = 1.45 (95% CI: 0.77, 2.76) for $ICNIRP_H^2$ and OR = 1.38 (95% CI: 0.75, 2.54) for $ICNIRP_E^2$, based on 19 and 17 exposed cases respectively. ORs for meningioma were somewhat smaller than for glioma in the same exposure category and time window, OR = 1.52 (95% CI: 0.65, 3.55) for (unweighted) RF H-fields based on 8 exposed cases; OR = 1.30 (95% CI: 0.58, 2.91) for $ICNIRP_E^2$, based on 9 exposed cases; and OR = 1.17 (95% CI: 0.48, 2.84) for $ICNIRP_H^2$, based on 7 exposed cases. Although some larger ORs for meningioma were found in other exposure groups for $ICNIRP_H^2$, these were inconsistent and more imprecise. There was no clear evidence for a positive exposure-response trend in any of the exposure lags and time-windows studied for either glioma or meningioma and the exposure metrics used.

In the continuous analyses, results from polynomials with or without log transformation of exposure did not indicate evidence of departure from linearity according to model fit. Thus, results for non-linear models had worse model fit values, based on AIC/BIC results, and/or less precision. Overall, there were no positive significant associations between cumulative exposure to (frequency-unweighted) RF H-fields (Table 5), $ICNIRP_H^2$ (Table S6) or $ICNIRP_E^2$ (Table S7) and glioma or meningioma risk in any exposure lag or time window (only results for 1-year lag and 1–4 years exposure time window shown). However, linear models using (frequency-unweighted) RF H-fields (Table 5) in the 1–4 years exposure time window showed elevated, though imprecise, ORs for both glioma: OR = 1.82 (95% CI: 0.75, 4.42), and meningioma: OR = 1.46 (95% CI: 0.37, 5.74), per one-unit increase of (unweighted) RF H-fields cumulative exposure (A/m-years), while results for $ICNIRP_E^2$ and $ICNIRP_H^2$ were generally null. The log-log model for meningioma and $ICNIRP_H^2$ in the 1–4 years exposure time window,

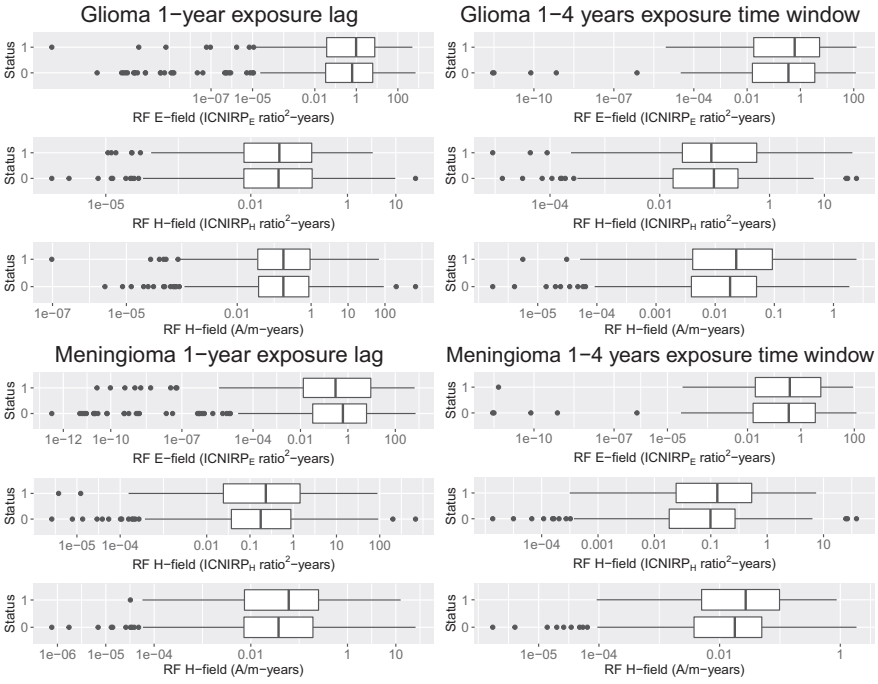

Fig. 1. Cumulative exposure to radiofrequency (RF) electric (E) and magnetic (H) fields (various metrics) by brain tumor type and exposure lag (overall exposure, 1-year lag) and time window (1–4 years exposure time window). Status (1 = cases; 0 = controls).

Table 3
Adjusted odds ratios (OR) and 95% confidence intervals for glioma or meningioma risk and cumulative RF E-field exposure ($ICNIRP_E$ ratio^2-years) for various exposure lags and time windows. INTEROCC study: Data from Australia, Canada, France, Germany, Israel, New Zealand and United Kingdom, 2000–2004.

RF E-field cumulative exposure (ICNIRP ratio^2-years)[b]	Glioma			Meningioma		
	Cases (*n*)	Controls (*n*)	OR[a] (95% CI)	Cases (*n*)	Controls (*n*)	OR[a] (95% CI)
1-year lag						
Non exposed[c]	1718	4734	1.00 (ref.)	1744	4566	1.00 (ref.)
< 0.63	102	277	0.75 (0.59, 0.96)	63	251	0.84 (0.62, 1.13)
0.63–6.21	57	135	0.82 (0.59, 1.14)	18	111	0.69 (0.41, 1.16)
6.22–40.6	40	82	0.92 (0.62, 1.37)	20	72	1.24 (0.73, 2.10)
≥40.7	24	55	0.87 (0.53, 1.44)	13	49	1.08 (0.57, 2.06)
5-year lag						
Non exposed	1718	4734	1.00 (ref.)	1744	4563	1.00 (ref.)
< 0.46	82	246	0.69 (0.53, 0.90)	54	223	0.84 (0.61, 1.15)
0.46–5.65	53	122	0.83 (0.59, 1.17)	20	103	0.80 (0.48, 1.31)
5.66–40.6	33	72	0.89 (0.58, 1.37)	20	61	1.51 (0.88, 2.57)
≥40.7	20	49	0.81 (0.47, 1.39)	11	44	1.01 (0.50, 2.03)
10-year lag						
Non exposed	1718	4734	1.00 (ref.)	1744	4563	1.00 (ref.)
< 0.27	66	212	0.64 (0.48, 0.86)	47	191	0.86 (0.61, 1.21)
0.27–4.92	38	104	0.73 (0.50, 1.08)	18	91	0.84 (0.50, 1.43)
4.93–34.6	30	63	0.92 (0.58, 1.45)	15	52	1.36 (0.74, 2.49)
≥34.7	17	43	0.79 (0.44, 1.42)	9	38	0.95 (0.44, 2.05)
5–9 years						
Non exposed	1718	4721	1.00 (ref.)	1744	4550	1.00 (ref.)
< 0.42	58	139	0.84 (0.61, 1.17)	22	124	0.60 (0.38, 0.97)
0.42–4.47	32	67	0.93 (0.60, 1.44)	18	53	1.48 (0.84, 2.61)
4.48–18.8	18	40	0.82 (0.46, 1.47)	8	38	1.08 (0.66, 2.39)
≥18.9	12	27	0.90 (0.44, 1.83)	6	23	1.03 (0.45, 2.63)
1–4 years						
Non exposed	1718	4721	1.00 (ref.)	1744	4553	1.00 (ref.)
< 0.36	48	139	0.69 (0.49, 0.98)	23	123	0.60 (0.38, 0.96)
0.36–3.45	30	69	0.85 (0.54, 1.35)	13	51	1.13 (0.60, 2.14)
3.46–13.6	18	42	0.77 (0.44, 1.37)	6	37	0.86 (0.35, 2.13)
≥13.7	19	27	1.38 (0.75, 2.54)	9	26	1.30 (0.58, 2.91)

[a] Odds ratios (ORs) from conditional logistic regression models, matched by 5-year age group, sex, country, and region, and adjusted by education. Confidence intervals (CIs) based on Wald test.
[b] Exposure categories based on irregular quantiles of the cumulative exposure distribution of controls (i.e. 50th, 75th, and 90th percentiles).
[c] Non-exposed cases and controls include only subjects who were never occupationally exposed (i.e. 1-year lag).

however, gave the best fit values and a weak but more precise non-significant positive association: OR = 1.20 (95% CI: 0.74, 1.94).

Fig. 2 shows the exposure-response relationship between RF E-fields ($ICNIRP_E^2$) cumulative exposure (overall and in the 1–4 years exposure time window) for glioma and meningioma, based on predicted risk estimates from two models (log-linear and translog-quadratic) as well as the ORs and 95% CIs from the categorical analysis for the same exposure lag or time window. Results for RF H-fields are presented in Figs. S2 (frequency-unweighted) and S3 (frequency-weighted). While predicted ORs in the 1–4 years exposure time window tended to be above 1.0 for both glioma and meningioma, ORs for overall exposure (1-year lag) were near 1.0 or below. Overall, the patterns using ORs from the categorical analysis resembled those from the continuous models.

Results for IF H-fields ($ICNIRP_H$-years) showed no clear suggestion of an association with either glioma or meningioma risk (Table S8) and were based on a small number of exposed participants (~1%). ORs were generally < 1.0 in the lowest exposure category (i.e. < median) for both glioma and meningioma. ORs above 1.0 were only observed in the highest exposure categories for the 1–4 and 5–9 years exposure time windows for glioma, while results for meningioma were not consistent.

In sensitivity analyses, exclusion of unresponsive subjects, subjects aged > 60 years, subjects with very low or very high cumulative exposure levels, proxy interviewees, and participants with a history of neurofibromatosis or tuberous sclerosis had little effect (< 10% change) on the ORs obtained (data not shown), neither did analysis of high- and low-grade glioma, separately (Table S9), or stratifying by sex (Table S10). Moreover, there was no evidence of effect modification or confounding by any of the factors considered, including mobile phone use, allergy history and exposure to medical ionizing radiation (data not shown). Restricting the analyses to exposed subjects only, using the lowest exposed category as the reference group for either RF E- and H-fields (Tables S11 and S12), resulted in positive ORs in most exposure categories, with no evidence of an exposure-response trend.

4. Discussion

This study, based on the analysis of nearly 4000 brain tumor cases and over 5000 controls, is the largest case-control study of brain tumors and occupational RF and IF-EMF exposure to date. The work on exposure assessment, based on a detailed source-based questionnaire and a source-exposure matrix specifically developed for the project is, to our knowledge, the most comprehensive effort aimed at estimating occupational exposure to high-frequency EMF in a large population-based epidemiological study. Overall, despite the major improvement in exposure assessment, the study provided no evidence for a positive association between cumulative RF or IF-EMF exposure and either glioma or meningioma risk, with risk estimates mostly < 1.0, and only some non-significant positive ORs in some exposure time windows for the highest exposed categories.

Previous studies examining associations of brain tumor risk and exposure to RF fields have not found clear results. A non-significant increase of brain cancer risk was observed in a study of radio operators (Milham, 1988), while studies of police officers (Finkelstein, 1998) and naval and aviation personnel (Groves et al., 2002) found non-statistically reduced risks for brain tumors. However, these studies had small numbers of cases and none of them looked at risk by level of exposure.

Table 4
Adjusted odds ratios (OR) and 95% CIs for glioma or meningioma risk and cumulative RF H-field exposure (A/m-years) for various exposure lags and time windows. INTEROCC study: Data from Australia, Canada, France, Germany, Israel, New Zealand and United Kingdom, 2000–2004.

RF H-field cumulative exposure (A/m-years)[b]	Glioma			Meningioma		
	Cases (*n*)	Controls (*n*)	OR[a] (95% CI)	Cases (*n*)	Controls (*n*)	OR[a] (95% CI)
1-year lag						
Non exposed[c]	1740	4803	1.00 (ref.)	1756	4629	1.00 (ref.)
< 0.04	99	243	0.77 (0.60, 1.00)	45	210	0.78 (0.56, 1.10)
0.04–0.18	52	119	0.85 (0.59, 1.17)	23	101	0.87 (0.55, 1.40)
0.19–0.65	29	69	0.91 (0.58, 1.43)	21	64	1.25 (0.74, 2.09)
≥0.66	21	49	0.92 (0.54, 1.57)	13	45	1.24 (0.64, 2.40)
5-year lag						
Non exposed	1740	4803	1.00 (ref.)	1756	4626	1.00 (ref.)
< 0.04	83	213	0.74 (0.56, 0.97)	40	184	0.83 (0.58, 1.19)
0.04–0.18	44	106	0.81 (0.56, 1.17)	23	93	0.92 (0.57, 1.49)
0.19–0.63	29	62	1.00 (0.63, 1.59)	18	55	1.24 (0.71, 2.17)
≥0.64	14	43	0.75 (0.40, 1.41)	11	40	1.25 (0.61, 2.55)
10-year lag						
Non exposed	1740	4803	1.00 (ref.)	1756	4626	1.00 (ref.)
< 0.04	69	182	0.75 (0.56, 1.01)	34	159	0.83 (0.56, 1.23)
0.04–0.16	30	89	0.65 (0.42, 1.01)	17	77	0.91 (0.52, 1.57)
0.17–0.62	27	54	1.08 (0.67, 1.75)	17	48	1.34 (0.74, 2.41)
≥0.63	9	37	0.54 (0.26, 1.15)	8	34	0.92 (0.41, 2.09)
5–9 years						
Non exposed	1740	4789	1.00 (ref.)	1756	4616	1.00 (ref.)
< 0.03	57	124	0.90 (0.65, 1.26)	25	103	0.88 (0.56, 1.40)
0.03–0.09	25	61	0.80 (0.49, 1.30)	12	57	0.89 (0.47, 1.69)
0.10–0.29	22	36	1.22 (0.71, 2.11)	9	32	1.17 (0.54, 2.54)
≥0.30	8	25	0.72 (0.31, 1.63)	6	23	1.24 (0.48, 3.22)
1–4 years						
Non exposed	1740	4789	1.00 (ref.)	1756	4616	1.00 (ref.)
< 0.02	49	124	0.79 (0.55, 1.11)	18	100	0.61 (0.36, 1.02)
0.02–0.04	21	65	0.64 (0.38, 1.06)	17	58	1.37 (0.78, 2.43)
0.05–0.12	17	34	0.94 (0.51, 1.71)	7	31	0.89 (0.37, 2.10)
≥0.13	19	25	1.62 (0.86, 3.01)	8	23	1.52 (0.65, 3.55)

[a] Odds ratios (ORs) from conditional logistic regression models, matched by 5-year age group, sex, country, and region, and adjusted by education. Confidence intervals (CIs) based on Wald test.
[b] Exposure categories based on irregular quantiles of the cumulative exposure distribution of controls (i.e. 50th, 75th, and 90th percentiles).
[c] Non-exposed cases and controls include only subjects who were never occupationally exposed (i.e. 1-year lag).

Table 5
Adjusted ORs for glioma and meningioma using continuous RF H-field cumulative exposure for 1-year lag and 1- to 4-year exposure time window, and various polynomial models. INTEROCC study: Data from Australia, Canada, France, Germany, Israel, New Zealand and United Kingdom, 2000–2004.

Model #	Model form	Odds ratio[a]	95% CI[b]	AIC[c]	BIC[d]
Glioma					
RF H-field cumulative exposure (A/m-years), 1-year lag					
1	Log-linear	0.91	0.74–1.13	7164.97	7181.69
2	Log-log	0.84	0.51–1.37	7165.58	7182.30
RF H-field cumulative exposure (A/m-years), 1- to 4-year exposure time window					
1	Log-linear	1.82	0.75–4.42	7164.44	7181.16
2	Log-log	2.15	0.55–8.46	7164.93	7181.65

Model #	Model form	Odds ratio[a]	95% CI[b]	AIC[c]	BIC[d]
Meningioma					
RF H-field cumulative exposure (A/m-years), 1-year lag					
1	Log-linear	0.99	0.87–1.13	6752.52	6769.11
2	Log-log	1.10	0.65–1.86	6752.43	6769.02
RF H-field cumulative exposure (A/m-years), 1- to 4-year exposure time window					
1	Log-linear	1.46	0.37–5.74	6752.28	6768.87
2	Log-log	1.98	0.29–13.3	6752.09	6768.68

[a] ORs from conditional logistic regression models, stratified by 5-year age group, sex, country, and region, and adjusted by education.
[b] Confidence intervals (CI) based on Wald test.
[c] AIC: Akaike Information Criterion.
[d] BIC: Bayesian Information Criterion. Note: only results for log-linear and log-log models are shown since more complex models were unstable due to limited data.

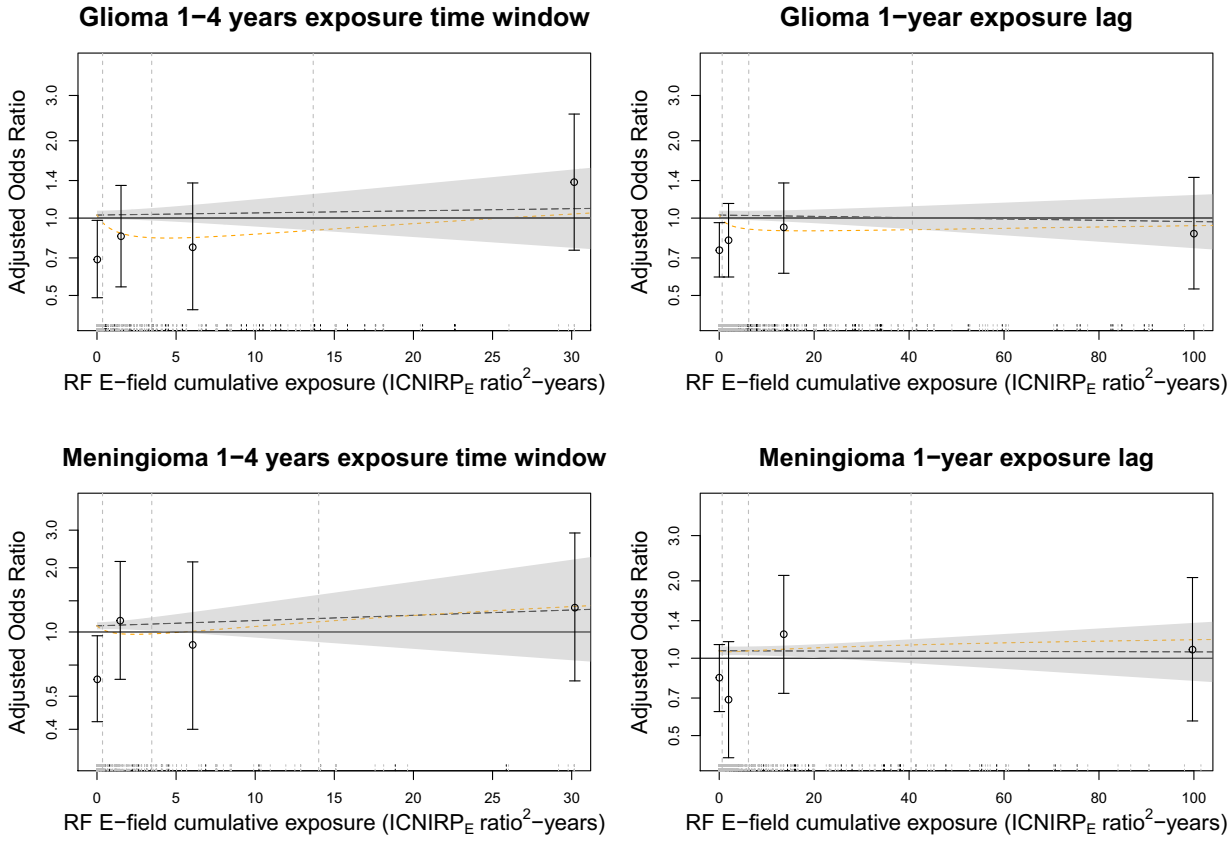

Fig. 2. Exposure-response relationship between risk of glioma and meningioma (ORs based on conditional logistic regression models, matched by 5-year age group, sex, country, and region, and adjusted by education) and (frequency-weighted) RF E-field cumulative exposure (ICNIRP$_E$ ratio^2-years) for overall exposure (1-year lag) and 1- to 4-year exposure time window. The dashed lines indicate the linear model (long dashes) and a quadratic model with log-transformed exposure (short dashes). The grey shadow indicates Wald-type 95% CIs for the linear model. Vertical dashed lines on the left side of the plot indicate the cut points used in the categorical analysis (i.e. 50th, 75th and 90th percentiles of the cumulative exposure distribution of controls). Points and error bars indicate adjusted ORs and Wald-type 95% CIs for the exposure categories based on these cut points. The ORs and CIs from the categorical analysis are positioned at the median exposure for each interval. Plot rug are cases (dashed short vertical black lines) and controls (dashed short vertical grey lines). Plots truncated at the 95th percentile of cumulative exposure to improve visibility.

In one case-control study (Grayson, 1996), semi-quantitative exposure estimates were assigned to male air force workers based on a detailed occupational history obtained through questionnaire. Although no overall association was found for exposure level and risk of brain cancer, a small excess risk was seen when comparing ever versus never exposed. Another brain tumor case-control study (Thomas et al., 1987), in which workers´ exposure was classified by expert industrial hygienists, found a significant increased risk among men exposed to RF for more than twenty years. A study in Australia in which researchers assessed glioma and RF exposure data, using a general job-exposure matrix, observed many reduced ORs (Karipidis et al., 2007).

An INTEROCC sub-study using the German study population (Berg et al., 2006) classified subjects according to their RF-EMF exposure likelihood based on their job titles. This study found several non-significant positive associations for occupational RF exposure and brain tumor risk. The OR for glioma in highly exposed subjects was 1.22 (95% CI: 0.69, 2.15) overall and 1.39 (95% CI: 0.67, 2.88) when only jobs conferring high exposure for more than ten years were considered. Similar results were obtained for meningioma, with ORs of 1.34 (95% CI: 0.61, 2.96) for overall exposure and 1.55 (95% CI: 0.52, 4.62) for ten years or more of high exposure jobs. Although our results in the categorical analysis are similar, with non-significantly increased ORs for highly exposed groups, the German study observed the increase in the 10+ years exposure group, while we observed an increase only in the most recent exposure time window.

Little information exists in the literature regarding exposure to high-frequency magnetic fields (H-fields) and risk of brain or other cancer types (SCENIHR, 2008; Sienkiewicz et al., 2010). In our analysis, we used both frequency weighted and unweighted RF and IF H metrics to account for potential thermal and non-thermal effects from exposure to H-fields. Both RF E- and H-fields are responsible for the energy absorbed in the body and could be associated with potential thermal effects (Hitchcock and Patterson, 1995). However, radical pair mechanisms, by which weak RF H-fields together with static fields could be responsible for the formation of reactive oxygen species, may promote the proliferation of cancer cells via non-thermal effects (Barnes and Greenebaum, 2016, 2015; Usselman et al., 2014). Therefore, since the absorbed energy hypothesis alone ignores other possible mechanisms by which RF and/or IF-EMF could lead to cancer, we also used (frequency-unweighted) RF H-fields in our analyses. Although results were not significant and imprecise, ORs for both H and ICNIRP$_H^2$ were slightly higher than those obtained using ICNIRP$_E^2$, which could reflect the lack of proportionality between E and H in the near field (ICNIRP, 1998). These differences are particularly important when assessing RF sources, such as glue dryers, plastic welding machines or climbing radio/TV towers, for which H are often the dominate fields (Eriksson and Hansson Mild, 1985; Hansson Mild, 1981; Hansson Mild and Mattson, 2017). Moreover, the results obtained using the frequency-unweighted RF H-field metric, although imprecise, provided the largest ORs, highlighting the need for further investigation. Results for IF H-fields were inconsistent and were based on low number of exposed subjects (~1%). Moreover, given the skewed exposure distributions,

there was little contrast between exposure categories used.

In the statistical analysis, we created conditional logistic regression models to obtain odds ratios of disease between cases and controls using the frequency-matched strata of the INTEROCC data. Although this was a significant change of the original individual matching used in INTERPHONE, we believe that the use of the conditional approach, recommended for matched data containing many strata with different number of cases and controls (Breslow and Day, 1980), ensured that valid effect estimates were obtained. For these analyses, we used both categorical and continuous exposure variables, including polynomials to test for departure from linearity (Royston et al., 2000). The linear model provided the best fit for our data based on AIC/BIC criteria (Hastie et al., 2008; Hosmer et al., 2013). Although more complex models, such as the translog-quadratic, gave worse fit results and/or wider confidence intervals, the similarities between this model and the results from the categorical analysis (as shown in Fig. 2) may support a J-shaped exposure-response hypothesis (Vrijheid et al., 2006). For the categorical analysis, considering the skewed nature of our data, we used irregular cut-points based on the 50th, 75th, and 90th percentiles of the distribution, as the best way to characterize the spread of the EMF distribution (Röösli and Vienneau, 2014). This approach allowed us to compare groups of subjects with similar exposure variability (GSD ≈ 2 in most groups). However, due to the small number of exposed participants (~10% for RF-EMF), the highest 10% of exposed subjects (> 90th percentile) represents < 1% of the study population. This limitation was also present in the German INTEROCC sub-study (Berg et al., 2006), where only ~11% of subjects were considered exposed. Moreover, although the German data are included in our analyses, the number of exposed subjects is still small and statistical power remains limited (Rothman and Greenland, 1998; Smith and Kriebel, 2010).

Our individualized exposure assessment approach entails an important improvement over previous efforts to assess high-frequency EMF exposure risks. The use of the recently constructed SEM (Vila et al., 2017) allowed us to assign estimates of RF and IF-EMF to each study subject on the basis of the EMF sources reported, increasing between-subject variability, compared to the use of JEMs (Rothman and Greenland, 1998; Smith and Kriebel, 2010; Sorahan and Swanson, 2017). Mean electric and magnetic field strength values in the SEM refer to the average level assigned to an RF or IF source based on measurements obtained from different countries and measured equipment, which could have different technical characteristics, including different frequency ranges. Therefore, the SEM mean estimates allowed assigning exposure levels to the EMF sources reported without knowing the technical characteristics of the equipment used, such as their specific frequency range, which was not available in INTEROCC. This methodology allows, therefore, assigning exposure estimates to subjects in other studies in which information on the EMF sources present in the workplace is available.

Exposure assessment of study participants was aimed at head exposure through the confidence weighting of the SEM estimates (Vila et al., 2017), which strengthens our approach to assess brain tumor risk. Thus, in the construction of the SEM, confidence ratings assigned to available measurements were used to calculate confidence-weighted mean exposure estimates for each RF or IF source in this matrix. Measurements were upweighted if they were representative of head exposure. Therefore, although some of the RF and/or IF sources reported by the study participants may lead to whole-body exposure, the confidence-weighted mean exposure levels used are our best estimates of local exposure of the head. However, the availability of measurements representative of head exposure differed by type of EMF source (Vila et al., 2017). Therefore, it is possible that the confidence-weighted estimates for some of the sources in the SEM may over- or underestimate exposure to the head. Nevertheless, it is likely that the potential bias introduced may have affected all subjects equally leading to non-differential misclassification and underestimation of effect estimates obtained (Rothman and Greenland, 1998).

The source-based individual approach used may have other limitations. Since the SEM does not contain exposure estimates from personal measurements for any RF source, estimates using other types of dosimetry (i.e. spot, 55%, and operator position, 45%) were used to calculate individual exposure. The use of such surrogates of personal exposure may have overestimated the assigned exposure levels, which, in turn, may have underestimated our risk results. Thus, although individual exposure assessment may reduce between-subject misclassification (i.e. Berkson error), it can also increase classical error (Kim et al., 2011; Tielemans et al., 1998). In addition, there is possibly residual Berkson error in our approach due to group-based exposure estimates in the SEM. These exposure assessment biases are, however, likely to be non-differential, possibly attenuating ORs towards no effect, although bias away from the null may have occurred from residual Berkson errors, particularly when considering more than two levels of exposure (Rothman and Greenland, 1998). Further improvements of the individualized EMF exposure assessment used in our study are, therefore, advisable, including the use of an improved SEM containing only personal estimates of exposure, when these become available.

Other weaknesses of this study include possible recall and selection biases. It is possible that our results may have been affected by recall error, particularly with regard to the impact of the disease on cases' ability to remember details of past jobs. Unlike the recall bias on details of past mobile phone use in the INTERPHONE studies (Cardis et al., 2011), we may assume it was easier for workers to recall the type of machinery used during their working lifetimes. Moreover, since subjects were generally unaware of exposure levels associated with the reported EMF sources, any recall bias is probably small, though random error could occur. Another weakness is the low participation rate among controls (53% vs 65% for glioma and 78% for meningioma cases), raising concerns about potential selection bias. Control participation was associated with socioeconomic status and with being a mobile phone user, and both could be associated with exposure to certain EMF sources. Such biases could be aggravated by the different protocols for subject selection and staff training among the INTERPHONE countries (Cardis et al., 2007). Selection bias and J-shaped exposure-response relationships, with reduced ORs at the lowest levels of cumulative exposure, were observed in the INTERPHONE study (Cardis et al., 2011; Vrijheid et al., 2009, 2006), and were attributed to under-selection of controls unexposed to mobile phones (Vrijheid et al., 2006). Although this particular form of selection bias is unlikely for this occupational EMF study, as discussed above, the reduced ORs obtained in the low exposure categories for both glioma and meningioma indicates that selection and/or recall biases could have possibly affected our findings.

Some studies have previously used ICNIRP-based metrics to assess integrated/cumulative exposure to RF fields (Baste et al., 2010; Heinrich et al., 2010; Thomas et al., 2008). However, ICNIRP-based exposure indices have several limitations. The term “ICNIRP ratio” is a metric for compliance with a regulatory limit, rather than an exposure metric with biophysical meaning, and there is little evidence to support that frequency-adjusted EMF using ICNIRP reference levels are a relevant exposure metric for cancer. Moreover, for the many different EMF exposure conditions found in workplaces, the cumulative ICNIRP metric is biased towards higher levels, since exposure limits are based on worst-case scenarios rather than average exposures (Durney et al., 1986; Hitchcock and Patterson, 1995). Therefore, although ICNIRP linear and squared ratios may be correlated with dose or dose rate, it is possible that exposure levels assigned to study participants were overestimated, which may have also contributed to the possible underestimation of our risk results.

In conclusion, despite the improved quantitative exposure assessment used in this study, the results do not support a positive association between occupational exposure to high-frequency EMF and either glioma or meningioma risk. However, given our limited statistical power, due to the small number of exposed participants, and despite

our results´ lack of significance (Greenland et al., 2016; Rothman, 2016; Smith and Kriebel, 2010), our findings foster the need for further research focusing on RF magnetic fields and tumor promotion, as well as possible interactions with other frequencies and with chemicals. Moreover, since most RF studies until now have focused on the effects of electric fields, more studies of RF magnetic fields are needed, particularly looking at differences between near-field (e.g. walkie-talkies) and far-field exposures (e.g. radars). Furthermore, the development of biology-based dose metrics which take into account both electric and magnetic fields from various sources (Hansson Mild and Mattson, 2017) may provide further insights on the potential biophysical mechanism (s), other than heating and nerve electro-stimulation (ICNIRP, 1998; IEEE, 2006), by which long-term exposure to high-frequency EMF may damage health.

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Disclaimer

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Conflict of interest

The authors have no conflicts of interest to declare.

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