Allergy and Brain Tumors in the INTERPHONE study: Pooled Results from Australia, Canada, France, Israel, and New Zealand

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ABSTRACT

Purpose: A history of allergy has been inversely associated with several types of cancer although the evidence is not entirely consistent. We examined the association between allergy history and risk of glioma, meningioma, acoustic neuroma, and parotid gland tumors using data on a large number of cases and controls from five INTERPHONE study countries (Australia, Canada, France, Israel, New Zealand), to better understand potential sources of bias in brain tumor case-control studies and to examine associations between allergy and tumor sites where few studies exist.

Methods: A total of 793 glioma, 832 meningioma, 394 acoustic neuroma, and 84 parotid gland tumor cases were analyzed with 2520 controls recruited during 2000-2004. Conditional logistic regression models were used to obtain odds ratios (ORs) and 95% confidence intervals (CIs) for associations between self-reported allergy and tumor risk.

Results: A significant inverse association was observed between a history of any allergy and glioma (OR = 0.73, 95% CI 0.60-0.88), meningioma (OR = 0.77, 95% CI 0.63-0.93), and acoustic neuroma (OR = 0.64, 95% CI 0.49-0.83). Inverse associations were also observed with specific allergic conditions. However, inverse associations with asthma and hay fever strengthened with increasing age of allergy onset and weakened with longer time since onset. No overall association was observed for parotid gland tumors (OR = 1.21, 95% CI 0.73-2.02).

Conclusions: While allergy history might influence glioma, meningioma, and acoustic neuroma risk, the observed associations could be due to information or selection bias or reverse causality.

Key words: asthma, hay fever, eczema, glioma, meningioma, acoustic neuroma

BACKGROUND

A history of allergy has been inversely associated with several types of neoplasm including brain tumors [1], although the evidence is not entirely consistent. A 2007 meta-analysis of eight studies, involving 3450 glioma and 1070 meningioma cases, reported significant inverse associations, with ORs ranging from 0.6 to 0.7, between a history of any allergy, asthma, eczema and glioma risk but no association with meningioma [2]. National analyses of INTERPHONE data in Germany and the UK reported inverse associations between allergy and risk of glioma and meningioma, but not acoustic neuroma [3-6]. An analysis of data from five INTERPHONE study countries (Denmark, Norway, Finland, Sweden, and southeast England) including 1527 glioma cases and 3309 control subjects reported significant inverse associations (0.65) with a history of asthma, hay fever, and eczema and a significant inverse trend with number of allergic conditions [7]. However, the inverse associations with hay fever and eczema were observed only for current disease and not for those who were clear of disease. No association was observed with acoustic neuroma [8]. Postulated biological mechanisms underlying an inverse association between allergy and cancer risk include enhanced immune function and surveillance, with possible roles for immunoglobulin E (IgE) and allergy-related cytokines [2,9].

However, results from studies with prospectively recorded histories of allergy are inconsistent with those from case-control studies. Results from two cohorts in the Swedish Twin Registry reported both inverse and null associations between allergy and glioma risk, as well as positive associations with meningioma; however there were few incident brain tumors observed [10]. No association was observed between a history of asthma or hay fever and overall brain cancer

mortality in the large-scale Cancer Prevention Study-II involving data on over 1.1 million participants and 2195 brain cancer deaths [11], possibly suggesting some form of reporting bias in case-control studies. There are also conflicting results in case-control studies according to timing of allergy diagnosis and the possibility of reverse causality remains of concern.

Given continued and expanding research into possible allergic influences in cancer [1,9], we sought to examine the association between allergy history and risk of glioma, meningioma, acoustic neuroma, and parotid gland tumors using data on a large number of cases and controls from a consortium of five other INTERPHONE studies (Australia, Canada, France, Israel, and New Zealand) with detailed data on the timing of allergy onset and other study-related factors, such as respondent type and interview quality, to better understand potential sources of bias in brain tumor case-control studies and to examine associations between allergy and tumor sites where few published studies exist, e.g., meningioma, acoustic neuroma, and parotid gland.

METHODS

Study Population

INTERPHONE is a large, 13-country, largely population-based case-control study conducted according to a common protocol. Detailed methods are published elsewhere [12,13]. Cases of primary brain glioma, meningioma, acoustic neuroma, and parotid gland tumors between 30 and 59 years of age at diagnosis were recruited between 2000 and 2004. Glioma, meningioma, and acoustic neuroma cases were identified among residents of major population centers in Australia

(Melbourne, Sydney), Canada (Montreal, Ottawa, Vancouver), France (Lyon, Paris), and New Zealand (Greater Auckland, Hamilton, Rotorua, Tauranga, Napier, Hastings, Wellington, Palmerston North, Christchurch). In Israel, the study was nationwide. Malignant parotid gland cases were recruited in Australia, Canada (all centers), and Israel, and benign parotid gland cases in Canada-Ottawa and Israel only. Incident cases were rapidly recruited from all major treatment centers (with the exception of Paris, where some centers did not participate), and completeness verified through secondary sources. All cases recruited were confirmed histologically or through unequivocal diagnostic imaging. Because of the more favorable prognosis of acoustic neuroma and parotid gland tumors, retrospective case ascertainment up to one year in the past was permitted for these rarer lesions to increase the statistical power of the study.

Controls were randomly selected from electoral lists (Australia, Canada-Montreal, France, New Zealand), health/population registries (Canada-Vancouver, Israel), or random digit dialing (Canada-Ottawa). The original INTERPHONE protocol called for the selection of one control for each case of glioma or meningioma, two controls for acoustic neuroma, and three controls for parotid gland tumors, matched according to five-year age groups, sex, region, and country of birth (Israel only). To maximize statistical power in this analysis, all eligible controls were matched post-hoc to case subjects separately using a matching algorithm that optimized interview time and age group within categories of sex, region, and country of birth (Israel only) [13]. The date of diagnosis for the case was used as the reference date for the control subject in each matched set. Written informed consent was obtained from all study participants prior to the interview. The median (range) number of controls matched to each case was 3 (2-20) for glioma, 3 (1-22) for meningioma, 4 (1-19) for acoustic neuroma, and 8 (2-62) for parotid gland tumors.

Data Collection

Eligible participants were interviewed by trained interviewers using a computer-assisted personal interview (CAPI) questionnaire. If the participant had died or was unable to participate, a proxy respondent was used. The questionnaire captured detailed information on a range of personal and family characteristics. Participants were asked to indicate if they had ever been diagnosed with asthma, hay fever, or eczema, and at what age (years) they experienced their first episode. For eczema, participants were also asked to indicate at what age (years) they stopped having the disease, what proportion of time they were affected, if their eczema appeared when they came in contact with particular substances, and what were the main agents that caused the disease. Participants were also asked if any of their close family members are affected by asthma, hay fever, or eczema.

Statistical Analysis

Conditional logistic regression models were used to obtain adjusted ORs and 95% CIs characterizing the association between allergy history and brain tumors in all five studies combined. Models were stratified by country, region, sex, and five-year age group at the reference date and adjusted for level of educational attainment (high school or less, medium level technical or professional school, university graduate). The independent effect of a history of any allergy diagnosed at least one year prior to the diagnosis or reference date was examined, as well as that of specific allergic conditions (asthma, hay fever, eczema). The reference category

consisted of participants with no diagnosis of asthma, hay fever, or eczema. The mid-point of the reported age at first episode was used where an age range was reported for analyses according to categories of age or time since onset. Adjustment for marital status (single, married, other), cigarette smoking (cigarette smoking status, cigarettes per day, years smoked), and interview year was also attempted, but produced virtually no change (<10%) in regression coefficients (results not presented).

To assess potential reporting biases, sensitivity analyses were conducted examining only self-reported data (excluding proxy interviews), participants who had a high quality interview (as determined by the interviewer), and participants with only in-person interviews (excluding telephone interviews). Sensitivity analyses were also conducted including only study centers with a population-based recruitment strategy, or with higher control response rates (≥ 60%). Multiplicative interaction terms between allergy history and country, sex, age at reference date (< 50 years, ≥ 50 years), and smoking status (ever, never) were entered into the conditional logistic regression models to assess potential effect modification, with two-sided P-values calculated based on the likelihood ratio statistic.

Analyses were conducted using SAS version 9.2 [14]. Ethics approval was obtained from the Ottawa Hospital and from all appropriate national and local research ethics boards as well as from the Ethical Review Board of the International Agency for Research on Cancer (IARC, Lyon) for the INTERPHONE study and of the Municipal Institute for Medical Investigation (IMIM) Barcelona for maintenance and exploitation of the five-country database at CREAL.

RESULTS

Out of a total of 3141 eligible cases (1302 gliomas, 1199 meningiomas, 521 acoustic neuromas, and 119 parotid gland tumors), 2132 were interviewed (809 gliomas, 842 meningiomas, 397 acoustic neuromas, and 84 parotid gland tumors) and formed part of a matched set [13]. Following exclusions of participants with missing data on allergy or educational attainment, 793 glioma, 832 meningioma, 394 acoustic neuroma, and 84 parotid gland tumor cases were retained for analysis; the total number of control subjects ranged from 1074 for parotid gland tumors to 2374 for gliomas.

Table 1 presents selected participant characteristics at enrollment. Glioma cases were more likely to be male (63.3%) and meningioma cases female (74.9%). Meningioma cases also tended to be somewhat older at diagnosis and have a lower level of educational attainment. A total of 17.4% of glioma cases were interviewed by proxy, whereas proxy interviews were less frequent for other tumor types.

A history of any allergy was reported by 25.8% (32.9%) of glioma cases (controls), 26.8% (32.8%) of meningioma cases (controls), and 26.3% (35.6%) of acoustic neuroma cases (controls). For parotid gland tumors (not shown), respective percentages were 35.7% among cases and 26.8% among controls.

There was a significant inverse association between a history of any allergy and risk of glioma (OR = 0.73, 95% CI 0.60-0.88), meningioma (OR = 0.77, 95% CI 0.63-0.93), and acoustic

neuroma (OR = 0.64, 95% CI 0.49-0.83) but not parotid gland tumors (OR = 1.21, 95% CI 0.73-2.02) (Table 2). The inverse association was somewhat stronger in those with a family history of any asthma, hay fever, or eczema for glioma (OR = 0.69, 95% CI 0.54-0.87), but not for meningioma (OR = 0.77, 95% CI 0.62-0.97) or acoustic neuroma (OR = 0.67, 95% CI 0.49-0.91). A history of both personal and family history of allergy was reported by 17.7% (23.8%) of glioma cases (controls), 19.7% (24.2%) of meningioma cases (controls), and 19.6% (26.9%) of acoustic neuroma cases (controls).

Inverse associations were also observed according to specific allergic conditions (Table 2). For asthma, ORs ranged from 0.68 for acoustic neuroma to 0.77 for meningioma; only for glioma was the OR significantly reduced. For hay fever, ORs ranged from 0.67 for glioma to 0.80 for meningioma, with significant reductions for both glioma and acoustic neuroma. For eczema, the reduced ORs (ranging from 0.56 to 0.74) were statistically significant for all three outcomes. ORs were somewhat reduced for a history of contact eczema (glioma OR = 0.60, 95% CI 0.36-1.01; meningioma OR = 0.76, 95% CI 0.49-1.17; acoustic neuroma OR = 0.65 95% CI 0.35-1.22). ORs for all three outcomes tended to be lower among subjects reporting a history of all three allergic conditions.

However, there was some evidence that the inverse associations with asthma and hay fever strengthened with increasing age of allergy onset and weakened with longer time since onset (Table 2). For eczema, the inverse associations tended to be stronger in those with current disease (glioma OR = 0.52, 95% CI 0.33-0.82; meningioma OR = 0.69, 95% CI 0.47-1.00; acoustic neuroma OR = 0.46 95% CI 0.26-0.84) compared to those whose eczema symptoms had

ceased (glioma OR = 0.84, 95% CI 0.57-1.24; meningioma OR = 0.86, 95% CI 0.59-1.25; acoustic neuroma OR = 0.71 95% CI 0.41-1.23).

The inverse associations with allergy were generally stronger for high-grade than low-grade glioma (Table 3). Moreover, there was an inverse gradient in the risk of high grade glioma with number of allergies - although no similar gradient was apparent for low grade gliomas.

Upon restriction to participants with a history of asthma only (44 cases, 130 controls), with no history of hay fever or eczema, the inverse association between asthma and glioma was attenuated (OR = 0.92, 95% CI 0.63-1.33), but persisted for meningioma (OR = 0.72, 95% CI 0.49-1.05) and acoustic neuroma (OR = 0.61 95% CI 0.35-1.08). For participants with a history of hay fever only (75 cases, 270 controls) or eczema only (32 cases, 154 controls), results did not materially change (hay fever only - glioma OR 0.73, 95% CI 0.54-0.97; meningioma OR 0.76, 95% CI 0.56-1.02; acoustic neuroma OR 0.63, 95% CI 0.42-0.94; eczema only - glioma OR 0.68, 95% CI 0.45-1.03; meningioma OR 0.69, 95% CI 0.48-0.99; acoustic neuroma OR 0.55, 95% CI 0.33-0.93).

Sensitivity analyses restricting data to participants who were self-respondents, who had a high quality interview, and who were interviewed in-person produced little change in ORs (Table 4). Results were also insensitive to the exclusion of data from Paris, where recruitment was not completely population-based. However, when restricting the analysis to centers with higher control participation rates (≥ 60%), the inverse relationship for glioma was somewhat attenuated, while those for meningioma and acoustic neuroma were somewhat strengthened.

There was no significant modification of associations by sex, age at reference date, or cigarette smoking status (results not shown); except that for the association between a history of hay fever and meningioma the OR was 0.61 (95% CI 0.44-0.87) in never smoking participants and 1.10 (95% CI 0.77-1.57) in ever smokers (P value for interaction = 0.01). There was no evidence that results varied by country (P values for interaction ranging from 0.75 to 0.89).

DISCUSSION

We report in a large-scale international case-control study with data on 2103 case and 2520 control subjects, apparent risk reductions of 30% for glioma, 20-30% for meningioma, and 30-40% for acoustic neuroma with a history of any allergy and histories of specific allergic conditions. These inverse associations tended to strengthen for asthma and hay fever in those with an older age at allergy onset and, reciprocally, for those with a more recent allergy. For eczema, inverse associations tended to be stronger in those with current compared to past disease. No association was observed for parotid gland tumors.

Although previous case-control studies have reported inverse associations between history of allergy and glioma, and, to a lesser extent, meningioma, there are conflicting results according to timing of diagnosis of allergy. An early six-country case-control study of 1178 glioma cases and 2493 control subjects reported significant inverse associations between a history of any allergy, eczema, other allergies and glioma risk (~ 40% reduction), but there was no trend according to

age at diagnosis or disease duration [15]. Similar results were reported by two smaller US studies [16,17].

However, the German-INTERPHONE study reported inverse associations between any allergy, hay fever, eczema and glioma with an older age at onset or shorter duration of allergy [3]. The Southeast and Northern UK INTERPHONE study also reported significant inverse associations between a history of any allergy and glioma (~40% reduction) as well as with specific allergic conditions which were stronger for those with a recent onset of asthma or eczema [5]. However, for meningioma, the strongest inverse associations were reported for those with an early age of asthma or hay fever onset (< 10 years) [6]. For the UK and Nordic studies combined, inverse associations (~40-50% reductions) between current but not prior allergy, hay fever, eczema and glioma risk were observed, but there was no trend according to age at onset or duration of the condition [7]. We had no data on whether asthma or hay fever symptoms had ceased. A case-control study in the San Francisco Bay Area also reported inverse associations between late-onset (12+ years) respiratory allergy and glioma [18].

There are fewer studies of acoustic neuroma. Brenner et al. [17] in a US case-control study of 96 cases and 799 controls, reported a significant positive association between a history of hay fever and acoustic neuroma (OR = 2.36, 95% CI 1.38-4.03), which was stronger with an older age at diagnosis or shorter disease duration. Combined results from the UK and Nordic INTERPHONE studies indicated no association between a history of allergy and acoustic neuroma overall or according to disease duration [8].

Findings of inverse associations strengthening in those with both an older age at allergy onset and more recent allergy here and in previous national analyses of INTERPHONE data may be due to either the importance of recent immunological status for cancer or conversely, the suppression of allergic symptoms by the developing tumor, or some combination of both. For glioma, both local and systemic immunosuppression is observed [19-20]. Schwartzbaum et al. [19] observed widespread down-regulation in allergy and inflammation gene expression with increasing glioblastoma progression in an analysis of microarray tissue sample data from 142 patients; however longitudinal data are needed. It is unlikely however, that reverse causality can explain findings at other tumor sites with minimal immunosuppressive effects. There are also allergic and non-allergic forms of asthma, hay fever, and eczema with distinct clinical and immunological features and asthma diagnosed later in life is more likely non-allergic compared to asthma diagnosed during childhood [21-22].

In this study strong inverse associations with allergy were observed for each of glioma, meningioma, and acoustic neuroma (but not parotid gland tumors), three tumors with distinct clinical and pathogenic profiles, possibly suggesting some sort of reporting bias in retrospective allergy ascertainment by case and control participants. Further, in support of a reporting bias explanation are results from studies with prospectively collected data on allergy history. The Swedish Twin Registry observed both inverse and null associations between allergy history and glioma risk, as well as positive associations with meningioma [10]. There was also no association observed between a history of asthma or hay fever and overall brain cancer mortality in the large-scale Cancer Prevention Study-II [11]. However there was no data on the timing of diagnosis or duration of allergy. Allergy history may be underreported by proxy respondents for

glioma cases [10]; however results here and in a previous meta-analysis were insensitive to the exclusion of proxy interviews [2]. There is also the possibility of cognitive impairment for high-grade glioma cases leading to underreporting of prior allergies. However, results were similar when examining only subjects with a high quality interview. Results were also of a comparable magnitude across all three tumor sites. The prevalence of any allergy (ranging from 25.8-35.7% of cases and 26.8-35.6% of controls) is similar to that reported in previous studies [23].

To address potential reporting biases, some studies have examined biological indicators of allergic status [18, 24-27]. A case-control study of 169 glioma cases and 520 controls nested in four prospective cohorts reported a significant inverse association between borderline (OR = 0.63, 95% CI 0.42-0.93) but not elevated total IgE levels. There was also no association with food- or respiratory-specific IgE [26]. A case-control study of 275 glioma, 175 meningioma, and 49 acoustic neuroma cases, and 963 control subjects nested in the European Prospective Investigation into Cancer (EPIC) reported an inverse association between elevated respiratory-specific IgE concentrations and glioma (OR = 0.73, 95% CI 0.51-1.06) but not meningioma or acoustic neuroma [27]. More recently, in a nested case-control study of 594 glioma cases and 1177 matched controls in Norway, significant inverse associations were observed between elevated respiratory-specific IgE concentrations and glioblastoma risk among women (OR = 0.46, 95% CI 0.23-0.93) and total IgE concentrations and glioma risk in both men and women combined, both overall (OR = 0.75, 95% CI 0.56-0.99) as well as for concentrations 20 years prior to diagnosis (OR = 0.54, 95% CI 0.30-0.99) [28]. However, questions regarding the utility of this biomarker remain, including typically low levels of concordance with self-reported allergy and changing levels of IgE over time [18,24,29,30]. Other studies examined

concentrations of immune regulatory proteins [31] or polymorphisms in allergy-related genes in relation to glioma risk [32-38]. In two studies, the inverse association between allergy and glioma was modified by genotype [33,35].

There may also be potential selection biases, particularly as response rates in the INTERPHONE study tended to be low among controls (ranging from 35-74%). In previous research, a meta-analysis of studies of childhood leukemia reported that inverse associations observed with allergy history were attenuated when restricting the analysis to studies with case and control response rates of ≥ 80% [39]. When we considered only centers with higher control response levels here (defined as ≥ 60%), results were attenuated for glioma, but strengthened for acoustic neuroma; differences however, were small. There was also a tendency for controls to be more highly educated than case subjects, however adjustment for level of education here resulted only in modest changes in ORs.

We lacked data on allergy medication use. Scheurer et al. [40] reported a significant three-fold increase in glioma risk for those with a history of long-term antihistamine use and a prior asthma or allergy history in a US case-control study of 325 glioma cases and 600 control subjects.

In conclusion, we observed inverse associations between a history of allergy and the risk of glioma, meningioma, and acoustic neuroma, but possible information or selection bias and reverse causality, cannot be ruled out as possible explanations for these findings. Further work is needed including sufficiently large studies with detailed prospectively-collected information on

indicators of allergy, allergy onset and cessation, and allergy medication use including multiple specific biomarkers of allergy and immune function.

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Table 1. Characteristics of participant case and control subjects at enrollment, INTERPHONE study countries: Australia, Canada, France, Israel, and New Zealand.

	Glioma		Meningioma		Acoustic Neuroma		Parotid Gland	
	Cases (n = 793)	Controls (n = 2374)	Cases (n = 832)	Controls (n = 2252)	Cases (n=394)	Controls (n=1436)	Cases (n=84)	Controls (n=1074)
Characteristic	%	%	%	%	%	%	%	%
Sex								
Male	63.3	45.8	25.1	41.9	50.3	47.3	50.0	47.5
Female	36.7	54.3	74.9	58.1	49.8	52.7	50.0	52.6
Age at reference date								
<=34	9.2	5.9	3.9	4.7	4.8	5.8	11.9	8.3
35-39	10.7	10.5	6.0	9.6	11.9	10.9	17.9	8.4
40-44	16.7	15.8	12.6	14.7	17.3	16.1	19.1	13.7
45-49	17.2	17.8	21.2	19.5	20.1	19.2	11.9	17.0
50-54	22.8	24.7	28.1	25.0	24.9	24.4	20.2	22.3
55+ years	23.5	25.3	28.3	26.6	21.1	23.6	19.1	30.5
Education								
High School or less	43.0	40.4	51.1	40.3	47.5	41.4	41.7	36.5
Medium level technical school	25.6	23.9	23.6	24.1	23.6	23.5	31.0	23.9
University	31.4	35.8	25.4	35.6	28.9	35.1	27.4	39.6
Country								
Australia	37.1	28.1	30.1	28.6	32.2	43.3	8.3	5.7
Canada	21.1	25.1	11.3	23.5	21.3	23.3	67.9	48.7
France	11.7	18.7	16.8	18.6	27.7	14.8	0.0	-
Israel	19.9	22.2	36.1	24.6	15.0	16.6	23.8	45.6
New Zealand	10.2	6.0	5.8	4.8	3.8	2.0	0.0	-
Interview location								
Hospital	13.2	0.7	16.8	0.7	6.1	0.4	2.4	0.8
Home	74.7	68.8	73.3	69.3	68.5	68.1	66.7	70.9
Other/missing	12.1	30.5	9.9	29.9	25.4	31.5	31.0	28.3
Proxy interviews	17.4	0.4	2.0	0.4	0.2	0.4	2.4	0.2

Table 2. Adjusted ORs (95% CIs) for glioma, meningioma, and acoustic neuroma in relation to a history of any allergy or specific allergic condition (asthma, hay fever, eczema), INTERPHONE study countries: Australia, Canada, France, Israel, and New Zealand.

	Glioma				Meningioma				Acoustic Neuroma			
Allergy	Cases	Controls	OR	95% CI[a]	Cases	Controls	OR	95% CI[a]	Cases	Controls	OR	95% CI[a]
No allergy	567	1580	1.00 (ref)	-	602	1497	1.00 (ref)	-	288	915	1.00 (ref)	-
Any allergy	197	774	0.73	(0.60-0.88)	220	731	0.77	(0.63-0.93)	103	505	0.64	(0.49-0.83)
No allergy	567	1557	1.00 (ref)	-	602	1461	1.00 (ref)	-	287	911	1.00 (ref)	-
Asthma	74	275	0.72	(0.54-0.96)	82	260	0.78	(0.59-1.03)	36	171	0.68	(0.45-1.02)
Age at onset												
<10 years	30	87	0.85	(0.55-1.33)	25	81	0.87	(0.54-1.40)	16	51	0.99	(0.53-1.82)
10-19 years	15	39	0.86	(0.45-1.64)	16	39	1.23	(0.65-2.33)	5	21	0.63	(0.23-1.75)
20+ years	29	146	0.58	(0.38-0.89)	41	138	0.64	(0.44-0.94)	14	93	0.52	(0.28-0.95)
Time since onset												
<10 years	9	64	0.38	(0.18-0.79)	21	57	0.81	(0.48-1.38)	7	45	0.54	(0.24-1.24)
10-19 years	14	60	0.60	(0.32-1.12)	12	54	0.47	(0.24-0.91)	7	33	0.65	(0.28-1.51)
20+ years	51	148	0.89	(0.63-1.26)	49	145	0.89	(0.62-1.26)	22	85	0.77	(0.46-1.29)
No allergy	567	1575	1.00 (ref)	-	602	1496	1.00 (ref)	-	288	895	1.00 (ref)	-
Hay Fever	115	457	0.67	(0.53-0.86)	130	428	0.80	(0.63-1.01)	64	299	0.68	(0.49-0.94)
Age at onset												
<10 years	28	79	0.93	(0.58-1.49)	21	75	0.74	(0.44-1.25)	10	38	1.15	(0.54-2.46)
10-19 years	39	136	0.69	(0.47-1.02)	45	131	1.03	(0.71-1.51)	15	92	0.45	(0.24-0.81)
20+ years	48	238	0.56	(0.40-0.79)	64	216	0.68	(0.50-0.94)	38	156	0.74	(0.49-1.10)
Time since onset												
<10 years	11	86	0.31	(0.16-0.61)	14	69	0.46	(0.25-0.85)	11	51	0.60	(0.30-1.20)
10-19 years	22	81	0.75	(0.45-1.23)	19	73	0.59	(0.35-1.02)	12	53	0.74	(0.38-1.45)
20+ years	82	286	0.75	(0.57-1.00)	96	277	0.95	(0.72-1.24)	40	181	0.70	(0.47-1.03)
No allergy	567	1562	1.00 (ref)	-	602	1448	1.00 (ref)	-	287	874	1.00 (ref)	-
Eczema	62	287	0.67	(0.49-0.91)	82	272	0.74	(0.56-0.98)	34	165	0.56	(0.37-0.85)
Age at onset												
<10 years	19	83	0.66	(0.38-1.12)	21	74	0.70	(0.42-1.19)	11	40	0.90	(0.44-1.83)
10-19 years	13	58	0.67	(0.36-1.25)	23	56	1.01	(0.60-1.69)	11	34	0.84	(0.41-1.71)
20+ years	30	145	0.70	(0.46-1.08)	38	142	0.65	(0.44-0.96)	11	89	0.31	(0.16-0.60)
Time since onset												
<10 years	8	48	0.57	(0.26-1.26)	16	50	0.88	(0.48-1.61)	6	37	0.40	(0.16-0.99)
10-19 years	14	53	0.64	(0.34-1.19)	10	49	0.45	(0.22-0.91)	3	29	0.28	(0.08-0.92)

20+ years	40	182	0.71	(0.49-1.03)	56	172	0.78	(0.56-1.09)	25	97	0.71	(0.43-1.15)
No allergy	567	1580	1.00 (ref)	-	602	1497	1.00 (ref)	-	288	915	1.00 (ref)	-
One allergy	151	562	0.77	(0.62-0.96)	157	530	0.74	(0.59-0.91)	75	369	0.63	(0.47-0.85)
Two allergies	38	167	0.63	(0.43-0.93)	52	159	0.88	(0.62-1.24)	25	110	0.74	(0.46-1.19)
Three allergies	8	45	0.53	(0.24-1.14)	11	42	0.77	(0.38-1.57)	3	26	0.35	(0.10-1.21)

[a] OR estimated using conditional logistic regression models stratified by country, region, sex, and five-year age group at the reference date and adjusted for level of educational attainment.

Table 3. Adjusted ORs (95% CIs) for high-grade and low-grade glioma in relation to a history of any allergy or specific allergic conditions (asthma, hay fever, eczema), INTERPHONE study countries: Australia, Canada, France, Israel, and New Zealand.

	High-grade glioma				Low-grade glioma			
Allergy	Cases	Controls	OR	95% CI[a]	Cases	Controls	OR	95% CI[a]
No allergy	379	1505	1.00 (ref)	-	186	1366	1.00 (ref)	-
Any allergy	123	736	0.69	(0.55-0.87)	72	649	0.77	(0.57-1.04)
No allergy	379	1475	1.00 (ref)	-	186	1283	1.00 (ref)	-
Asthma	43	259	0.62	(0.43-0.88)	30	215	0.89	(0.58-1.37)
Age at onset								
<10 years	24	81	0.99	(0.61-1.62)	6	70	0.55	(0.23-1.31)
10-19 years	6	37	0.55	(0.22-1.35)	9	31	1.44	(0.62-3.34)
20+ years	13	136	0.37	(0.20-0.67)	15	105	0.97	(0.54-1.76)
Time since onset								
<10 years	8	115	0.23	(0.11-0.50)	4	49	0.50	(0.17-1.47)
10-19 years					10	41	1.45	(0.67-3.12)
20+ years	35	139	0.92	(0.61-1.37)	16	117	0.86	(0.49-1.52)
No allergy	379	1505	1.00 (ref)	-	186	1309	1.00 (ref)	-
Hay Fever	72	437	0.64	(0.48-0.86)	42	370	0.70	(0.48-1.02)
Age at onset								
<10 years	15	74	0.78	(0.43-1.42)	13	67	1.14	(0.59-2.23)
10-19 years	23	128	0.61	(0.38-0.99)	15	113	0.78	(0.43-1.42)
20+ years	34	217	0.59	(0.40-0.88)	14	179	0.51	(0.28-0.91)
Time since onset								
<10 years	6	76	0.26	(0.11-0.62)	5	63	0.45	(0.17-1.17)
10-19 years	14	73	0.67	(0.36-1.24)	8	61	0.94	(0.43-2.08)
20+ years	52	275	0.73	(0.53-1.03)	29	235	0.73	(0.47-1.13)
No allergy	379	1493	1.00 (ref)	-	186	1345	1.00 (ref)	-
Eczema	32	273	0.53	(0.36-0.79)	29	230	0.93	(0.60-1.45)
Age at onset								
<10 years	9	78	0.45	(0.22-0.93)	10	63	1.12	(0.54-2.33)
10-19 years	7	53	0.55	(0.24-1.24)	6	44	0.85	(0.35-2.05)
20+ years	16	129	0.58	(0.33-1.02)	13	105	0.95	(0.50-1.80)
Time since onset								
<10 years	6	38	0.68	(0.28-1.69)	9	79	0.72	(0.34-1.52)
10-19 years	7	47	0.51	(0.23-1.17)				
20+ years	19	174	0.50	(0.30-0.83)	20	140	1.10	(0.66-1.85)
No allergy	379	1505	1.00 (ref)	-	186	1366	1.00 (ref)	-
One allergy	101	536	0.78	(0.60-1.00)	49	462	0.73	(0.51-1.03)
Two allergies	22	200	0.45	(0.28-0.72)	17	151	0.81	(0.47-1.40)
Three allergies					6	36	1.18	(0.48-2.91)

[a] OR estimated using conditional logistic regression models stratified by country, region, sex, and five-year age group at the reference date and adjusted for level of educational attainment. Note some adjacent cells collapsed due to small sample sizes in individual cells.

Table 4. Sensitivity analysis of adjusted ORs (95% CIs) for glioma, meningioma, and acoustic neuroma in relation to a history of any allergy according to interview and recruitment characteristics, INTERPHONE study countries: Australia, Canada, France, Israel, and New Zealand.

	Glioma				Meningioma				Acoustic Neuroma			
Allergy	Cases	Controls	OR	95% CI[a]	Cases	Controls	OR	95% CI[a]	Cases	Controls	OR	95% CI[a]
Baseline analysis												
No allergy	567	1580	1.00 (ref)	-	602	1497	1.00 (ref)	-	288	915	1.00 (ref)	-
Any allergy	197	774	0.73	(0.60-0.88)	220	731	0.77	(0.63-0.93)	103	505	0.64	(0.49-0.83)
Self-respondents												
No allergy	475	1553	1.00 (ref)	-	589	1484	1.00 (ref)	-	287	910	1.00 (ref)	-
Any allergy	178	767	0.76	(0.62-0.93)	216	729	0.76	(0.62-0.92)	103	504	0.64	(0.49-0.83)
High quality interviews only												
No allergy	445	1393	1.00 (ref)	-	503	1342	1.00 (ref)	-	259	805	1.00 (ref)	-
Any allergy	155	683	0.71	(0.57-0.89)	180	651	0.77	(0.62-0.95)	93	435	0.66	(0.50-0.87)
In-person interviews												
No allergy	558	1523	1.00 (ref)	-	598	1444	1.00 (ref)	-	279	878	1.00 (ref)	-
Any allergy	195	748	0.73	(0.60-0.88)	216	706	0.76	(0.62-0.92)	101	487	0.65	(0.50-0.85)
Population-based[b]												
No allergy	522	1380	1.00 (ref)	-	533	1299	1.00 (ref)	-	223	816	1.00 (ref)	-
Any allergy	178	639	0.73	(0.59-0.90)	190	601	0.79	(0.64-0.97)	81	439	0.68	(0.50-0.91)
Higher response rates[c]												
No allergy	261	934	1.00 (ref)	-	397	939	1.00 (ref)	-	169	486	1.00 (ref)	-
Any allergy	74	381	0.80	(0.59-1.08)	101	373	0.74	(0.56-0.96)	47	217	0.55	(0.38-0.82)

[a] OR calculated using conditional logistic regression models stratified by country, region, sex, and five-year age group at the reference date and adjusted for level of educational attainment.
[b] France (Paris) excluded.
[c] Australia, Canada (Vancouver), New Zealand excluded.

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