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Approaching a Scientific Consensus on the Association between Allergies and Glioma Risk: A Report from the Glioma International Case-Control Study

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Abstract

Background—Several previous studies have found inverse associations between glioma susceptibility and a history of allergies or other atopic conditions. Some evidence indicates that respiratory allergies are likely to be particularly relevant with regard to glioma risk. Using data from the Glioma International Case-Control Study (GICC), we examined the effects of respiratory allergies and other atopic conditions on glioma risk.

Methods—The GICC contains detailed information on history of atopic conditions for 4533 cases and 4171 controls, recruited from 14 study sites across five countries. Using two-stage random-effects restricted maximum likelihood modeling to calculate meta-analysis odds ratios, we examined the associations between glioma and allergy status, respiratory allergy status, asthma, and eczema.

Results—Having a history of respiratory allergies was associated with an approximately 30% lower glioma risk, compared to not having respiratory allergies (mOR: 0.72, 95% CI: 0.58–0.90). This association was similar when restricting to high-grade glioma cases. Asthma and eczema were also significantly protective against glioma.

Conclusions—A substantial amount of data on the inverse association between atopic conditions and glioma has accumulated, and findings from the GICC study further strengthen the existing evidence that the relationship between atopy and glioma is unlikely to be coincidental.

Impact—As the literature approaches a consensus on the impact of allergies in glioma risk, future research can begin to shift focus to what the underlying biological mechanism behind this association may be, which could, in turn, yield new opportunities for immunotherapy or cancer prevention.

Keywords

glioma; glioblastoma; allergies; asthma; eczema

Introduction

Over the past several decades, a history of allergies and atopic conditions has been consistently reported to be associated with decreased glioma risk (1–7). With some exceptions (8–10), the majority of studies have found that allergic conditions may reduce glioma risk by as much as 20–40% (1–4, 7). These associations have been examined using single- [i.e., (11)], multi-site [i.e., (12–14)], and nested case-control studies [i.e., (15, 16)], prospective cohort studies [i.e., (3)], and meta-analyses [i.e., (1, 2, 7)]. Additionally, the observed inverse association between allergies and glioma has remained consistent across studies with different exposure assessment strategies, such as self-reported allergy status (3), self-reported physician-diagnosed allergies (12, 13, 17–19), number of allergy types (12, 17), and allergy-related biomarkers, such as Immunoglobulin E [overall (4, 11, 16, 20), pre-diagnostic (16, 21), and/or allergen-specific (11, 15, 16)], soluble CD23 levels (22), and polymorphisms in allergy-related genes (23–26). As the literature approaches a consensus on the relationship between allergies and glioma risk, our large consortium, the Glioma International Case-Control Study (GICC), provides an unprecedented opportunity to not only confirm the previously reported associations between atopy and glioma in the largest available study population, but also to hone in on the specific role of respiratory allergies.

In studies that have examined specific allergy types, the observed associations between glioma and respiratory allergies (hay fever/allergic rhinitis) or asthma tend to be among the more robust (12, 15, 16, 20, 27–29). While reactions to food allergens are often limited to the gut (or systemic in the worst cases), inhaled allergens activate mucosal mast cells in the nasal passage and respiratory tract, and usually induce a localized response (30). The nasal passage may be of particular interest in studies of glioma, as some intranasally administered peptides or chemicals can cross the blood-brain barrier (BBB) (20, 31). Furthermore, particles of a certain size, charge, and configuration may enter the brain directly from the nasal passage through the trigeminal nerve sheath, bypassing the BBB (32, 33). Thus, it has been hypothesized that intranasal exposures are more likely to directly impact intracranial immune responses than food or contact allergies (16, 20).

In this international multi-site consortium study, we assessed the role of allergies (particularly respiratory allergies), asthma, and eczema on glioma risk. We also evaluated whether regular oral antihistamine use or respiratory allergy treatment type was associated with glioma risk. Our study represents the largest study of these associations to date (n= 4533 cases and 4171 controls), with the exception of a few meta-analyses of the previous literature (1, 7).

Materials and Methods

Study Population

Detailed information on the GICC study can be found elsewhere (34). Briefly, the GICC is an international consortium with 14 recruitment sites across five countries: Brigham and Women's Hospital (MA, USA), Case Western Reserve University (Ohio, USA), Columbia University (NY, USA), Danish Cancer Society Research Centre (Copenhagen, Denmark), The Gertner Institute (Tel Hashomer, Israel), Duke University (NC, USA), University of Texas MD Anderson Cancer Center (TX, USA), Memorial Sloan Kettering Cancer Center (NY, USA), Mayo Clinic (MN, USA), NorthShore HealthSystem (IL, USA), Umeå University (Umeå, Sweden), University of California, San Francisco (CA, USA), University of Southern California (CA, USA) and The Institute of Cancer Research (London, United Kingdom). Cases were defined as individuals within 18–80 years of age (at diagnosis) who had a histologically-confirmed, supra-tentorial, intracranial glioma [fibrillary astrocytoma (9420/3), protoplasmic astrocytoma (9410/3), gemistocytic astrocytoma (9411/3), oligodendroglioma (9450/3), oligoastrocytoma (9382/3), anaplastic astrocytoma (9401/3), anaplastic oligodendroglioma (9451/3), anaplastic oligoastrocytoma (9382/3), gliosarcoma (9442/3), and glioblastoma (9440/3)]. They were recruited within a year of diagnosis and consented at their clinic visits.

Controls were eligible for the study if they were between 18 and 80 years old. Because it was not feasible for all sites to recruit controls using identical methods, seven sites recruited visitors accompanying cancer patients as controls, four sites recruited clinic-based controls, and three sites used population-based controls.

All sites received Institutional Review Board (IRB) or ethical board approval to conduct the study, and informed consent was obtained from participants.

Data Collection

All sites adhered to a common study protocol and administered the same questionnaire. Study coordinators were centrally trained to help standardize data collection procedures. Data were stored in a centralized database. More information on data collection and reliability is provided elsewhere (34).

The GICC risk factor questionnaire included information on demographics, past medical/medication history, and occupational exposure history. Questionnaires were administered in-person and/or by phone, or through mailed self-administered forms. Regarding allergies and atopy specifically, the participants were asked about their experiences ≥1 year prior to brain tumor diagnosis (or enrollment). Allergy status was assessed by asking if the person experienced certain symptoms (skin, respiratory, watery eyes, digestive problems, anaphylaxis, or other) and whether he/she demonstrated allergic reactions to any of a list of potential allergens (dust/mold, plants/pollens, foods, animals, medications, soaps/cosmetics, or other). For each allergen, the participant was asked the age at first allergic episode (age <12, 12–20, or >20 years) and how they treated that particular allergy (medication, desensitization shots, epinephrine shots, avoidance, etc.). Participants were also asked about

asthma and eczema. Similar to allergies, they reported their age at first diagnosis and treatment method for each.

Detailed information on antihistamines and other allergy treatments was also collected. Participants were asked if they took antihistamines or decongestants regularly (once a month or more) for at least six months of their lives. We provided a list of the most commonly used allergy medications and also collected information on age at first allergy medication use.

Statistical Analysis

The overall GICC analysis plan (including sensitivity analyses) and a table of population demographics by study site has previously been published (34). For the current analyses, we compared cases and controls on relevant characteristics, overall, by study site, and by tumor grade (high-grade: WHO Grade IV; lower-grade: Grade II and III) among cases. Exposures of interest included: any allergies; respiratory allergies (defined as allergic rhinitis symptoms or allergic reactions to dust/mold or plants/pollens); allergies to animals/insects, food, medications, or soaps/cosmetics; allergy treatment severity; history of asthma; history of eczema; and long-term (≥6 months) oral antihistamine use. Analyses for each exposure of interest were conducted in the overall study population and separately by tumor grade.

Site-specific crude and adjusted odds ratios (ORs), along with their corresponding 95% Wald confidence intervals (CIs), were calculated for each exposure-outcome relationship, using unconditional logistic regression. Sites with less than five cases or controls in the exposed or unexposed groups were excluded from the meta-analyses. Data from Columbia University were omitted from the analyses due to a suspected data collection error that resulted in the prevalence of atopy being substantially lower among Columbia controls (6.4%) compared to all other sites and the national average.

Two-stage random-effects restricted maximum likelihood (REML) modeling was used to aggregate estimates across study sites into overall meta-analysis ORs (mORs) (34). For each REML model, the I^2 statistic was calculated to assess the percentage of variability in the effect estimates due to heterogeneity, rather than sampling error. The tau^2 statistic was used to evaluate the between-site variance, and the heterogeneity test p-value was computed. Forest plots were constructed as a visual representation of the site-specific (and overall meta-analysis) estimates. Analyses were conducted using SAS 9.2 (SAS Institute, Cary, NC) and R version 3.1.2.

We decided *a priori* to control for age and sex in our multivariable models, although doing so made virtually no difference to the effect estimates. Throughout our analyses, we also considered education, cigarette smoking, family history of brain tumors, and race/ethnicity as potential confounders, but none of these factors proved to be confounders in our data (based on a 10% change-in-estimate criterion) and were, thus, not included in the final models. Through stratified analyses, we explored the possibility of effect modification of allergy status by each of the following factors: sex, geographic location, asthma status, and long-term antihistamine use. We also conducted several sub-analyses stratifying by category of age at first allergic episode.

Because we had no direct measure of allergy severity, we examined the effects of treatment type, as an indirect measure of allergy severity. We constructed three treatment groups: high (treatments for pre-anaphylaxis/anaphylactic shock), medium (treatments for more moderate symptomologies), and mild/none (treatments for either mild or no symptoms). The high treatment group was defined by use of at least one of the following: desensitization shots, hospitalization, or epinephrine shot. The medium group was defined by use of allergy medications. The mild/no treatment group was defined by allergen avoidance or no treatment.

Although our analyses focused on the history of respiratory allergies, other allergy types (food, animal, medication, soap/cosmetic), asthma, and eczema were also evaluated separately. The impact of regular long-term oral antihistamine use on glioma risk was explored among those with and without allergies, as some individuals may take antihistamines regularly for indications other than allergic conditions (i.e., as sleep aids or antiemetics).

Despite our large sample size, our exploratory analyses of the potential interaction between respiratory allergies and asthma were underpowered, and thus, had to be analyzed by pooling the data from all sites, rather than by meta-analysis. While we acknowledge that pooling is not entirely appropriate given the inter-site heterogeneity present in our large consortium, these pooled analyses were exploratory in nature and were used to ascertain whether there may be some indication of an interaction at play that should be examined in future studies.

We conducted sensitivity analyses including and excluding proxy respondents and comparing the results to ensure that there were no meaningful discrepancies in ORs. Potential differences in ORs between sites by the different control types (visitor, clinic-, or population-based) were also examined to confirm that patterns by control type were not present in our results.

Results

The GICC includes a total of 4533 cases and 4171 controls recruited across 14 study sites. Table 1 presents the distributions of demographics and relevant attributes by case-control status and tumor grade. The age distribution between cases and controls was similar, but high-grade cases tended to be older than lower-grade cases, as expected. Cigarette smoking distribution was similar among cases and controls, with a slightly higher preponderance of current smokers among controls.

Overall, a history of any allergy was associated with a 21% lower risk of glioma, adjusting for age and sex, though this association was of borderline statistical significance (mOR: 0.79, 95% CI: 0.61–1.02) [data not shown]. UCSF was the only site in which a significant positive association was observed. Stratified by tumor grade, the association between any allergies and glioma was only significant among high-grade cases (mOR: 0.75, 95% CI: 0.58–0.98; among lower-grade, mOR: 0.84, 95% CI: 0.63–1.11). Geographic differences in the impact of allergies on glioma risk were not observed.

Figure 1 provides the site-specific and meta-OR for the association between *respiratory* allergies and glioma risk, overall (A) and by tumor grade (B & C). Overall, having respiratory allergies was associated with an approximately 30% lower glioma risk, compared to not having respiratory allergies (mOR: 0.72, 95% CI: 0.58–0.90). When stratifying by sex, the mOR remained remarkably similar among males (mOR:0.69, 95% CI:0.53–0.89), but among females, the effect was slightly attenuated (mOR:0.79, 95% CI:0.63–0.98) [not shown].

The association between respiratory allergies and glioma risk remained similar when restricting to high-grade gliomas (mOR:0.70, 95% CI: 0.57–0.85), whereas the magnitude of the effect was closer to the null and not statistically significant among lower-grade gliomas (mOR: 0.80, 95% CI: 0.62–1.03) [Fig. 1B&C]. When stratifying by age at glioma diagnosis/enrollment (<40, 40–59, and ≥60 years), the confidence intervals for the estimates overlapped between the three age groups and no obvious trends were seen (overall or by tumor grade).

Age of diagnosis of respiratory allergies was also considered in our analyses (Suppl. Table 1). When stratifying by age at allergy diagnosis prior to 20 years, the mOR between respiratory allergies and glioma was still in the inverse direction (mOR= 0.76, 95% CI: 0.58–1.00) and the confidence intervals largely overlapped with those of the mOR among allergies diagnoses at ages ≥20 (mOR= 0.67, 95% CI:0.54–0.83). Restricting the analyses to respiratory allergies diagnosed in early childhood (<12 years of age) yielded similar, though attenuated, results (mOR: 0.82, 95% CI: 0.64–1.06).

None of the other allergy types were significantly associated with glioma risk (Table 2), even among individuals without respiratory allergies [not shown].

The site-specific and overall associations between asthma status and glioma risk are provided in Figure 2. Fewer of the site-specific ORs were significantly protective against glioma, compared to the results for respiratory allergies, but overall, asthma was associated with a statistically significant 23% decreased glioma risk (mOR: 0.77, 95% CI: 0.64–0.93). Results were similar stratified by tumor grade (among high-grade, mOR: 0.76, 95% CI: 0.60–0.97; among lower-grade, mOR:0.73, 95% CI:0.58–0.92).

Due to small numbers, we could not examine the potential joint effects of asthma and respiratory allergies using meta-regression. However, when the data were pooled, our results suggested that having both asthma and respiratory allergies together (compared to having neither) may potentially confer slightly greater protection than having only asthma or only respiratory allergies [not shown]. However, as the pooled analysis does not account for inter-site heterogeneity, those results may be due to statistical fluctuations in our data.

A history of eczema was significantly associated with a decreased glioma risk, adjusting for age and sex (mOR:0.71, 95% CI: 0.56–0.89) [Fig. 3]. The effect of eczema was similar stratified by tumor grade (among high-grade, mOR:0.70, 95% CI:0.52–0.95; among lower-grade, mOR:0.69, 95% CI:0.53–0.90).

The association between long-term antihistamine use and glioma risk was not statistically significant, adjusting for age, sex, and respiratory allergy status (mOR:0.87, 95% CI:0.71–1.07). Restricting to individuals with respiratory allergies did not meaningfully change the mOR between long-term antihistamine use and glioma risk (mOR:0.90, 95% CI:0.74–1.09). We could not reliably evaluate this association among those without respiratory allergies due to small numbers. No differences by treatment type were observed.

Discussion

To our knowledge, our study represents the largest study to date on the role of allergic conditions in glioma risk. Using data from our international consortium, we found that respiratory allergies, asthma, and eczema were all significantly associated with reduced glioma risk. Our results are concordant with three previously published meta-analyses (1, 2, 7), as well as another large international multi-site consortium study (12), all estimating a 20–40% lower risk of glioma associated with having allergic conditions. The mORs reported in our study for overall allergies and respiratory allergies fall within this range. Similarly, our effect estimates for asthma and eczema are also consistent with these and other smaller studies (14, 27, 28, 35). Based on the growing body of evidence in the literature, the scientific community may be approaching a consensus on the role of allergies in glioma risk (36, 37).

While our study confirms several previous reports of the protective effect of allergies against glioma (1, 2, 5, 7), our data suggest that respiratory allergies may largely be driving the association we observed between general self-reported allergy status and glioma risk. Prior studies that have examined specific allergy types have also described similar protective effects associated with respiratory allergy, allergic rhinitis, or hay fever (1, 3, 18, 27). For example, combining effect estimates from five different studies, Chen et al. provided a meta-analysis OR of 0.78 (95% CI: 0.70–0.87) for hay fever and glioma risk (1). A series of cohort studies have also suggested that hay fever/allergic rhinitis may be protective against glioma, although results from these studies did not reach statistical significance (likely due to small numbers of cases) (3). Additionally, a case-control study nested in the European Prospective Investigation into Cancer and Nutrition Cohort (EPIC) found an OR of 0.73 for having specific IgE against the eight most common respiratory allergens (using pre-diagnostic specimens), though this finding was not statistically significant (95% CI: 0.51–1.06) (15). Similarly, Wiemels et al. reported an odds ratio of 0.73 (95% CI: 0.56–0.96) associated with a positive history of at least one self-reported respiratory allergy (20). Their results also implied that elevated respiratory IgE may be protective against glioma (OR: 0.80, 95% CI: 0.60–1.06). Although the latter finding did not attain statistical significance, their overall findings on respiratory allergies were more robust than those on food allergies, leading the authors to conclude that future research should focus specifically on the effects of respiratory allergies.

Like other studies (12, 15, 21), our study found that the protective effect of respiratory allergies (and any allergies) was stronger among high-grade glioma cases than it was for lower-grade cases. However, we have a larger sample size of high-grade cases (n=2722 versus n=1664 lower-grade), and the mOR for respiratory allergies was borderline

significant among lower-grade cases. Nevertheless, as other studies have also observed this pattern, future research should investigate why the effect of atopy may be more pronounced for high-grade gliomas.

Asthma and eczema were also found to be significantly protective against glioma risk in our study. Two major meta-analyses have estimated a 30% reduction in glioma risk for a positive history of either of these conditions (1, 2). Allergic rhinitis and asthma are both induced by inhaled allergens (30). Allergic rhinitis occurs when mucosal mast cells in the nasal epithelium are activated, whereas allergic asthma results from activation of the submucosal mast cells of the lower airways. Pathophysiologically, these two conditions both involve the respiratory tract, but asthma becomes characterized by chronic inflammation (even after the triggering allergen is no longer present). Eczema (or atopic dermatitis) is an allergic reaction in the skin, and like asthma, often involves persistent chronic inflammation. The fact that eczema demonstrates a similar inverse association with glioma as asthma and rhinitis may argue against that idea that reactions localized in the respiratory tract are more relevant to glioma etiology.

In our study, long-term antihistamine use was not significantly associated with glioma risk, adjusting for respiratory allergy status. The impact of antihistamine use is difficult to disentangle from that of allergies, as these factors are highly correlated, and few individuals without allergies use antihistamines regularly. Previously, McCarthy et al. reported an OR of 0.76 for the association between any oral antihistamine use versus none (95% CI: 0.59–0.99), but they did not adjust for allergy status and their result could, therefore, be confounded by the effect of allergies (17). In our prior studies, we have observed an increased risk for glioma associated with antihistamine use, particularly among individuals with allergic conditions (38–40); however, other studies have found either no association or a protective effect (18, 41). More detailed analyses on antihistamine use (accounting for frequency, duration, and type) are planned, and may help clarify this relationship.

As the literature approaches a consensus on the impact of allergies in glioma risk, future research can begin to shift focus to what the underlying biological mechanism behind this association may be, and eventually, whether this mechanism may be exploited to provide new avenues for immunotherapy or cancer prevention. One commonly proposed hypothesis on how allergies may confer protection against glioma revolves around the idea that allergies and other atopic conditions may represent a heightened state of immunosurveillance (2, 11, 17, 42). The presence of a hyperactive immune system may subsequently prohibit abnormal cell growth or proliferation, but the specific mechanism by which heightened immunosurveillance could help abate tumor growth remains unexplained. While the fact that allergies appear to reduce risk of some other cancers, such as pancreatic cancer, may lend credibility to this hypothesis, it is unclear why, then, allergies would increase risk for certain other cancers, such as bladder cancer (4, 6).

Another proposed explanation for the inverse association between allergies and glioma risk is that IgE antibodies against certain allergens may display some cross-reactivity to brain tumor antigens (16, 43). Most studies on IgE levels and antigen-specific IgE have isolated these antibodies from serum. Thus, information on whether serum IgE levels and subtypes

reflect the IgE levels and subtypes in the brain would be useful in assessing the plausibility of this hypothesis.

Allergies (and IgE) are thought to have evolved as a defense against macro-parasite infestation, but it also has been argued that the Th2-IgE mediated allergic response has a key role in protecting against environmental toxins (i.e., irritants, venoms, and other harmful xenobiotics) (44–46). Therefore, another possible explanation for the protective effect of allergies against glioma involves the idea that individuals with stronger allergic responses are more successful at expelling and/or disarming environmental toxins or carcinogens over the course of their lives (16, 45). This hypothesis would be especially interesting if future analyses continue to find that *respiratory* allergies, specifically, are of key importance in decreasing glioma risk.

Epidemiologic studies are also still warranted to clarify other related topics. For example, what proportion of the protective effect of allergies against glioma risk is attributable specifically to respiratory allergies deems clarification. Although a few well-designed studies have examined respiratory allergen-specific IgE levels (15, 20), many additional studies are needed before the impact of respiratory versus other allergy types can truly be disentangled. Furthermore, innovative markers of respiratory-specific allergies may be needed, as circulating IgE has a serum half-life of about two days (47) and can be difficult to measure during the relevant etiologic time period (which itself remain unknown and should be examined in prospective studies).

There are also many questions remaining regarding the role of antihistamines. Future research should investigate the effects of different generations of antihistamines and should also separately examine H2 receptor antagonists (i.e., cimetidine), given that the brain has H1, H2, and H3 receptors (31). The joint effects of using antihistamines in conjunction with steroids, decongestants, inhalers, or nasal sprays also warrant elucidation.

Our study has some limitations inherent to multi-site consortia. There is a substantial amount of site-to-site heterogeneity between our 14 sites; thus, we have provided the site-specific effect estimates for key analyses. Due to differences in infrastructure, resources, and institutional policies, different types of controls and questionnaire administration methods had to be used across sites. However, we conducted a series of sensitivity analyses [detailed in (34)] to ensure that control type or questionnaire administration method did not discernably bias the results presented here. Nonetheless, we are unsure why the site-specific OR from UCSF demonstrates a significant adverse association between respiratory allergies and glioma here, as previous UCSF studies have reported inverse associations similar to those observed at our other sites (11, 20, 42).

A common limitation in retrospective studies of glioma is the use of proxy respondents for cases who have cognitive impairment. The proportion of proxy responses in our study is low (<10%), and exclusion of proxy responses did not meaningfully change the results of our analyses. Furthermore, Chen et al. has previously provided evidence that the associations observed in case-control studies of atopy and glioma are unlikely to be due to bias from proxy reporting (1). A related issue is the possibility that glioma cases may not remember

past exposures accurately due to cognitive deficits. However, the associations reported here have also been found in prospective cohort studies, nested case-control studies, and meta-analyses of the existing literature (1–3, 7, 21).

A substantial amount of data on the inverse association between atopic conditions and glioma has accumulated (36, 37). In 2011, Davis and Al-Alem delineated the available evidence for each of Bradford-Hill's causal criteria in their commentary, suggesting that the current knowledge on atopy and glioma supports a potentially causal underlying relationship (36). Two of the most important concerns about the atopy-glioma relationship relate to the temporality of reported allergies (or lack of allergies) relative to glioma development and the idea that glioma cases may not accurately remember having atopic conditions, thus under-reporting them compared to controls. However, given the series of different study designs and exposure assessment tactics used to evaluate these associations, there is now at least some evidence to allay both of these concerns. The findings from the GICC study support the existing evidence that the relationship between atopy and glioma is unlikely to be coincidental. Thus, future research should begin to focus on clarifying the biological mechanisms contributing to this long-observed inverse relationship.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

GICC	Glioma International Case-Control Study
OR	odds ratio
mOR	meta-analysis odds ratio
BBB	blood-brain barrier

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Figure 1A

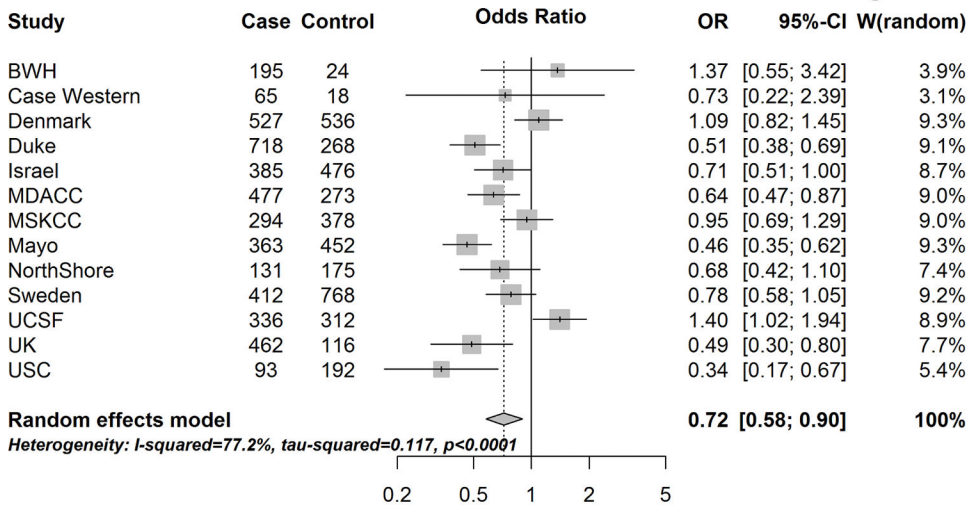
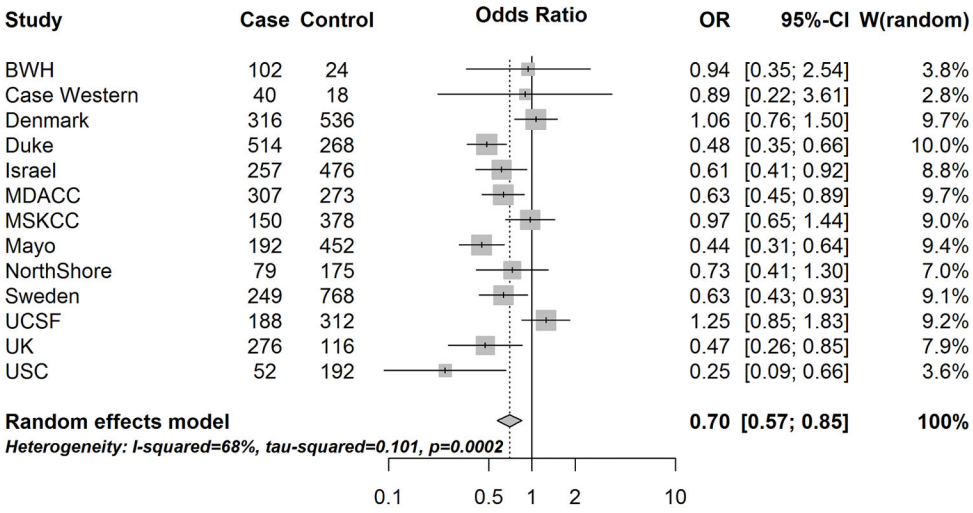


Figure 1B



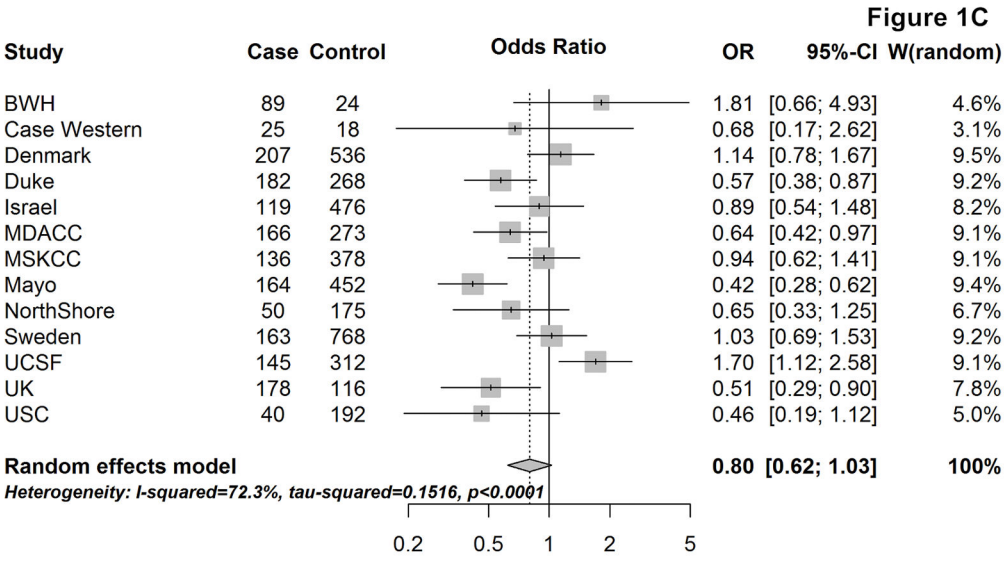


Figure 1.

Site-specific and meta-analysis odds ratios and 95% confidence intervals from the Glioma International Case-Control Study (GICC) for the association between history of respiratory allergies and glioma risk: overall (A), for high-grade glioma (B), and for lower-grade glioma (C). Meta-analysis odds ratio was calculated using restricted maximum likelihood modelling.

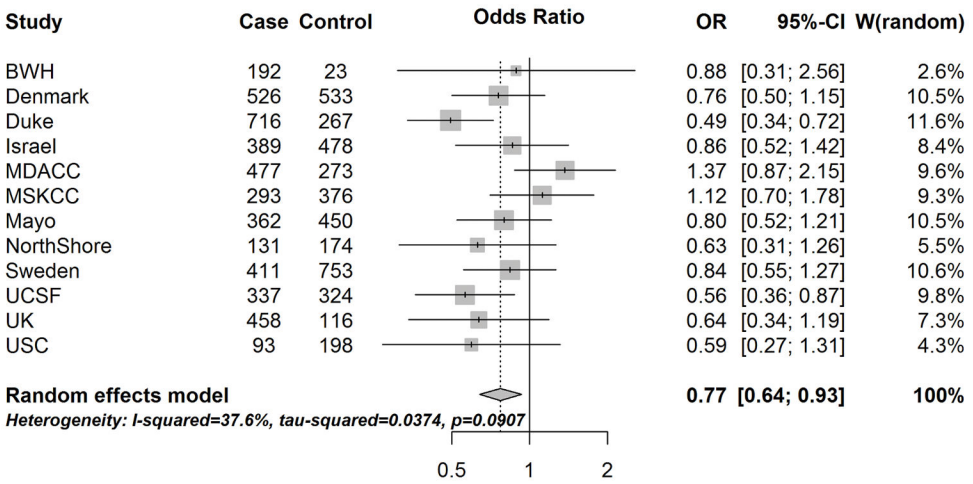


Figure 2.

Site-specific and meta-analysis odds ratios and 95% confidence intervals from the Glioma International Case-Control Study (GICC) for the associations between history of asthma and glioma risk. Meta-analysis odds ratio was calculated using restricted maximum likelihood modelling.

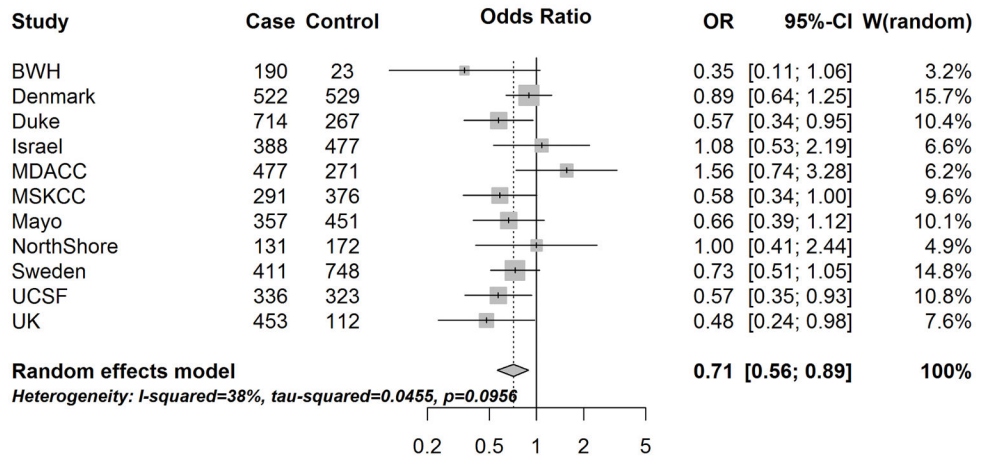


Figure 3.

Site-specific and meta-analysis odds ratios and 95% confidence intervals from the Glioma International Case-Control Study (GICC) for the associations between history of eczema and glioma risk. Meta-analysis odds ratio was calculated using restricted maximum likelihood modelling.

Table 1

Selected population characteristics from The Glioma International Case-Control Study (GICC) by case-control status and glioma grade

	Glioma Cases		Controls		High-Grade Glioma Cases[a]		Lower-Grade Glioma Cases[a]	
	N	%	N	%	N	%	N	%
Sex								
Male	2679	59.1	2351	56.37	1728	62.29	916	54.3
Female	1854	40.9	1820	43.63	1046	37.71	771	45.7
Diagnosis/enrollment age								
18–29 years	308	6.79	294	7.05	62	2.24	228	13.52
30–39 years	521	11.49	473	11.34	108	3.89	398	23.59
40–49 years	813	17.94	680	16.3	417	15.03	384	22.76
50–59 years	1150	25.37	1079	25.87	796	28.7	338	20.04
60–69 years	1239	27.33	1098	26.32	993	35.8	238	14.11
70–80 years	502	11.07	547	13.11	398	14.35	101	5.99
Education[b]								
High School or less	1126	27.67	911	22.47	716	28.66	392	25.99
Some college	1104	27.13	1293	31.89	651	26.06	433	28.71
Bachelor's degree	1020	25.06	955	23.55	595	23.82	409	27.12
Advanced degree	808	19.85	892	22	530	21.22	268	17.77
Missing	12	0.29	4	0.1	6	0.24	6	0.4
Smoking								
Never	2458	54.22	2271	54.45	1504	54.22	914	54.18
Current	440	9.71	468	11.22	236	8.51	195	11.56
Former	1581	34.88	1413	33.88	998	35.98	562	33.31
Missing	54	1.19	19	0.46	36	1.3	16	0.95
Respiratory allergy								
Yes	1547	34.13	1462	35.05	912	32.88	601	35.63
No	2966	65.43	2682	64.3	1847	66.58	1081	64.08
Missing	20	0.44	27	0.65	15	0.54	5	0.3

	Glioma Cases		Controls		High-Grade Glioma Cases[a]		Lower-Grade Glioma Cases[a]	
	N	%	N	%	N	%	N	%
Animal/insect allergies								
Yes	641	14.14	556	13.33	357	12.87	270	16
No	3759	82.93	3468	83.15	2340	84.35	1362	80.74
Don't know	63	1.39	79	1.89	36	1.3	26	1.54
Missing	70	1.54	68	1.63	41	1.48	29	1.72
Food Allergies								
Yes	398	8.78	437	10.48	223	8.04	162	9.6
No	4013	88.53	3599	86.29	2478	89.33	1476	87.49
Don't know	57	1.26	67	1.61	35	1.26	22	1.3
Missing	65	1.43	68	1.63	38	1.37	27	1.6
Medication allergies								
Yes	985	21.73	828	19.85	600	21.63	366	21.7
No	3412	75.27	3202	76.77	2098	75.63	1262	74.81
Don't know	71	1.57	76	1.82	40	1.44	30	1.78
Missing	65	1.43	65	1.56	36	1.3	29	1.72
Soap/cosmetics allergies								
Yes	317	6.99	327	7.84	187	6.74	121	7.17
No	4076	89.92	3691	88.49	2505	90.3	1508	89.39
Don't know	67	1.48	79	1.89	39	1.41	28	1.66
Missing	73	1.61	74	1.77	43	1.55	30	1.78
Long-term antihistamine use								
Yes	772	17.03	731	17.53	466	16.8	288	17.07
No	3750	82.73	3433	82.31	2304	83.06	1392	82.51
Don't know	10	0.22	4	0.1	4	0.14	6	0.36
Missing	1	0.02	3	0.07	0	0	1	0.06

[a]Sum of high-grade and lower-grade cases does not equal total number of cases, due to cases with unclassified tumors.

[b]Educational attainment information was not collected by one study site (The Institute of Cancer Research, London, UK).

Table 2

Associations between various allergy types and glioma risk: Results from the Glioma International Case-Control Study (GICC)

	Case		Control					Heterogeneity Test		
	N	%	N	%	Adjusted Meta-Analysis Odds Ratios (95% Confidence Intervals)[a]			I^2 (%)	Tau^2	P-value
Animal/insect allergies[b]								59.30	0.0761	0.0063
No	3783	85.55	3407	86.08	1.00					
Yes	639	14.45	551	13.92	0.98	0.80	1.21			
Food allergies[b]								66.10	0.1411	0.0011
No	4038	91.11	3540	89.17	1.00					
Yes	394	8.89	430	10.83	0.78	0.59	1.03			
Medication allergies								68.90	0.1004	0.0001
No	3443	77.91	3147	79.41	1.00					
Yes	976	22.09	816	20.59	0.98	0.80	1.21			
Soap/cosmetics allergies[c]								75.50	0.2607	<0.0001
No	4098	92.82	3629	91.83	1.00					
Yes	317	7.18	323	8.17	0.79	0.55	1.12			

[a] Full two-stage random-effect restricted maximum likelihood model adjusting for glioma diagnosis/enrollment age and sex.

[b] Case Western and USC excluded from meta-analysis due to cell frequencies <5.

[c] Brigham and Women's, Case Western, and USC excluded from meta-analysis due to cell frequencies <5.