Atopic disease is a hyperactive immune state that is traditionally characterized by T-cell production of high levels of cytokines such as interleukin (IL)-4 and IL-13, which belong to the T helper 2 (Th2) cytokine subclass, and an associated shift away from Th1 responses. Atopic diseases, including asthma, eczema, and allergy, have been related to lower risk of primary glioma in numerous epidemiologic studies (1–9). The association between atopic disease and meningioma has been less consistent (2,5,7,8,10). The absence of a consistent relationship between atopy and meningioma compared with that observed between atopy and glioma has been attributed to differences in disease etiology, smaller study sizes with insufficient power, or differences in proxy reporting, which is less common in studies of meningioma than in studies of glioma.

Several mechanisms have been proposed to explain the association between atopic disease and glioma. The findings may reflect a true causal effect of the heightened immune function seen in atopy on tumor development. For example, one hypothesis is that the hyperreactive state of the immune system in atopic individuals may result in increased immune surveillance and limit abnormal cell proliferation. Animal studies support a role for cytokines involved in atopy on brain tumor protection (11,12), and biomarkers of asthma are inversely related to glioma development (13,14).

Alternatively, the inverse associations observed may be noncausal and may arise from methodologic biases inherent in epidemiologic study design. These biases include possible selection bias due to inappropriate choice of controls or low control response rates, measurement error from self-reported allergy assessment, reverse causation, or confounding by unmeasured causes. Furthermore, a high frequency of exposure ascertainment by proxy may lead to bias, especially if proxies systematically underreport allergic disease (8). However, to fully explain the associations observed with glioma, at least some of these biases would have to be of substantial magnitude and to extend to multiple published studies.
We conducted a systematic literature review and meta-analysis of the association between atopic diseases and incidence of glioma and meningioma among international populations. In this article we summarize the scientific evidence from observational studies and quantify the magnitude of the observed effect.

**Methods**

**Search Strategy and Study Selection**

We searched MEDLINE, EMBASE, and ISI Web of Science from January 1979 through February 2007 using combinations of the search terms glioma, meningioma, brain tumor, atopy*, asthma, eczema, and allerg*. To be eligible for inclusion in this meta-analysis, publications had to include original data from case–control or cohort studies, to report on a medically confirmed outcome of primary glioma or meningioma, and to present an odds ratio or relative risk (RR) quantifying the association between atopic diseases including allergy, asthma, or eczema and primary glioma. We initially identified three cohort studies [reported in one publication (8) and nine case–control studies (1–7,9,12) that met our criteria and appeared to be relevant in assessing our hypothesis (Table 1). One of the cohort studies in Schwartzbaum et al. (8) combined varying exposures, including a hospital discharge diagnosis of diabetes or immunologic or allergic disease, and was therefore not included in any further analyses. We selected the most common definition of exposure among studies for adequate comparability. Allergy, asthma, and eczema were each evaluated as dichotomous exposures (yes or no) reflecting self-reported history of any versus no such condition. If data from a study appeared in more than one publication, we used the most recent publication for this analysis. Information on study design, participant characteristics, measurement of allergic disease, adjustment for potential confounders, percentage of study participants who reported exposure by proxy, and estimates of associations were extracted by two independent investigators (E. Linos and D. Michaud).

**Statistical Analysis**

Study-specific log relative risks (cohort studies) and log odds ratios (case–control studies) were weighted by the inverse of their variances to obtain a pooled relative risk estimate and its 95% confidence interval (CI). Odds ratios were considered to be estimates of relative risks. Random-effect models were used to statistically pool all estimates because in the absence of heterogeneity the random effects model exactly equals the fixed-effect model. We assessed heterogeneity among studies using the $Q$ test statistic of DerSimonian and Laird (15). Statistical evaluation of publication bias is difficult with few, small studies (16). We therefore assessed potential publication bias using sensitivity analysis and funnel plot symmetry (17) and calculated fail-safe numbers using a weighted method (18). The natural logarithm of the relative risk in each study was plotted against the inverse of its variance to obtain a funnel plot. A fail-safe number reflects the number of null studies of average precision that would need to be added to the meta-analysis to make the overall effect non–statistically significant (18,19). If the number of studies that is required to render the association non–statistically significant exceeds $5n + 10$, where $n$ is the original number of studies, publication bias is extremely unlikely (18). All analyses were conducted with STATA v. 9.2 (20). All tests of statistical significance were two-sided. Our report adhered to the Meta-analysis of Observational Studies in Epidemiology checklist for meta-analyses of observational research (21).

**Results**

A total of 12 studies of glioma and atopic disease were identified in our literature search (Table 1). Data from three case–control studies (2–4) were included in a subsequent larger international analysis (5); therefore, the smaller studies were excluded from our pooled analysis. As already noted, one of the three cohort studies in Schwartzbaum et al. (8) was excluded because of problems with exposure definition. Our final analysis included a total of 53223 participants and 3450 cases of glioma. Studies were conducted in seven countries, including Australia, Canada, France, Germany, Sweden, the United Kingdom, and the United States, between 1977 and 2004. All studies used medically confirmed primary glioma as the outcome and self-reported atopic disease as the exposure, although four studies (6,7,9,13) asked specifically about medically diagnosed atopic disease. Potential founders that were adjusted for in each study are shown in Table 2. All studies adjusted for age and sex, and some studies controlled for additional variables, including, race, location, and socioeconomic status, which are potential confounders. We did not find substantial evidence of heterogeneity among the studies of allergy and glioma ($P = .51$). The study-specific risk ratios ranged from 0.45 to 1.09 (Fig. 1). In the pooled analysis, those who reported a history of any allergy had a lower risk of glioma than those who reported no history.
of allergy (pooled RR = 0.61, 95% CI = 0.55 to 0.67, P<.001). Six studies (5–9,12) reported risks of glioma with respect to a history of asthma or eczema specifically. We did not detect statistically significant between-study heterogeneity for associations of glioma with asthma ($P = 0.72$) or with eczema ($P = 0.82$). The pooled RR for glioma among those reporting a history of asthma compared with no such history was 0.68 (95% CI = 0.58 to 0.80, $P<.001$) (Fig. 2). A similar inverse association with glioma was noted for a history of eczema ($RR = 0.69$, 95% CI = 0.58 to 0.82, $P<.001$).

**Proxy Reporting**

The participation of proxies is common in studies of progressive disease, and if reporting by proxy is systematically different from individual patient reporting it can lead to bias. Three case–control studies (4,6,9) provided relative risk estimates of the association between allergy and glioma with no or minimal data collection by proxy. Two of these studies (4,6) reported relative risks among the subsets of cases for whom self-reported information was available, and because the other study (9) did not have ethical permission to approach proxies, 98% of its cases were self-reported. Neither of the two cohort studies (8) described any reporting by proxy. The pooled relative risk estimate for all five studies without any proxy reporting remained inverse and statistically significant ($RR = 0.66$, 95% CI = 0.58 to 0.75).

**Publication Bias**

To assess the possibility of publication bias, we recalculated the pooled relative risk estimates for the association of glioma with allergy under the following extreme assumptions in a sensitivity analysis: 1) a similar number of unpublished studies have been performed; 2) these have analogous sample size and number of cases; but 3) they observed null results with relative risks of 1. Under these assumptions, the statistically significant inverse association between allergy and glioma persisted ($RR = 0.78$, 95% CI = 0.73 to 0.84, $P<.001$). In addition, a funnel plot of the results of studies examining the association between allergy and glioma (Fig. 3) was
symmetric, which implies that publication bias was unlikely. Finally, in the fail-safe analysis (18) the number of null studies that would need to be added to render the association of allergy with glioma non–statistically significant was 333, which exceeds the criterion of 45 ($5n + 10$).

**Meningioma**

Of the 12 studies identified originally, four case–control (2,5,7,9) and two cohort (8) studies reported on the association between a history of allergy and risk of meningioma. Because the data from one case–control study (2) were subsequently included in a larger international study (5), our pooled estimate does not include the smaller study. Medically confirmed cases of primary meningioma were recorded in all studies included (total N = 1070). Exposure was assessed by questionnaire or interview, as described above. The random-effects pooled estimate of these studies was not statistically significantly different from 1 (RR = 0.93, 95% CI = 0.72 to 1.19) (Fig. 4). The studies reporting on meningioma and allergy were somewhat heterogeneous in their results ($P = .09$). In a subanalysis that excluded the study with the largest relative risk (8), which was the most likely cause of this heterogeneity, the pooled risk ratio showed an inverse association between meningioma and allergy that was of borderline statistical significance (RR = 0.84, 95% CI = 0.72 to 0.98, $P = .029$).

### Table 2. Study-specific and pooled RR and 95% CIs for atopic disease and glioma*

<table>
<thead>
<tr>
<th>First author, date (reference)</th>
<th>Any allergy RR (95% CI)</th>
<th>Asthma RR (95% CI)</th>
<th>Eczema RR (95% CI)</th>
<th>Possible confounders adjusted for in analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schoemaker, 2006 (9)</td>
<td>0.63 (0.53–0.76)</td>
<td>0.71 (0.54–0.92)</td>
<td>0.74 (0.56–0.97)</td>
<td>Age (5-year groups), sex, location, interview year, SES (Townsend index)</td>
</tr>
<tr>
<td>Schwartzbaum, 2005 (13)$\dagger$</td>
<td>0.64 (0.33–1.25)</td>
<td>0.67 (0.43–1.05)</td>
<td>0.52 (0.19–1.48)</td>
<td>Age, sex</td>
</tr>
<tr>
<td>Schwartzbaum, 2003 (8)$\dagger$</td>
<td>1.09 (0.48–2.48)</td>
<td>1.06 (0.19–1.48)</td>
<td>0.92 (0.53–1.61)</td>
<td></td>
</tr>
<tr>
<td>Schwartzbaum, 2003 (8)$\dagger$</td>
<td>0.46 (0.14–1.48)</td>
<td>0.67 (0.43–0.92)</td>
<td>0.76 (0.45–1.27)</td>
<td>Age (10-year groups), sex, race, location, hospital distance (from hospital), hospital location</td>
</tr>
<tr>
<td>Brenner, 2002 (7)$\dagger$</td>
<td>0.67 (0.52–0.86)</td>
<td>0.63 (0.43–0.92)</td>
<td>0.76 (0.45–1.27)</td>
<td>Age (10-year groups), sex, race (white/nonwhite)</td>
</tr>
<tr>
<td>Wiemels, 2002 (6)$\dagger$</td>
<td>0.47 (0.33–0.67)</td>
<td>0.57 (0.38–0.86)</td>
<td>0.64 (0.47–0.86)</td>
<td>Age (5-year group), sex, location</td>
</tr>
<tr>
<td>Schlehofer, 1999 (5)$\dagger$</td>
<td>0.59 (0.49–0.71)</td>
<td>0.75 (0.55–1.03)</td>
<td>0.64 (0.53–1.04)</td>
<td>Age (5-year group), sex, location</td>
</tr>
<tr>
<td>Cicuttini, 1997 (4)</td>
<td>0.8 (0.5–1.4)</td>
<td>0.8 (0.5–1.4)</td>
<td>0.9 (0.5–1.4)</td>
<td>Age (5-year group), sex</td>
</tr>
<tr>
<td>Ryan, 1992 (2)</td>
<td>0.54 (0.33–0.89)</td>
<td>0.40 (0.14–1.15)</td>
<td>0.22 (0.05–0.92)</td>
<td>Age (2-year group), sex, location (postcode)</td>
</tr>
<tr>
<td>Schlehofer, 1992 (3)</td>
<td>0.7 (0.5–1.0)</td>
<td>0.68 (0.38–1.36)</td>
<td>0.70 (0.38–1.36)</td>
<td></td>
</tr>
<tr>
<td>Hochberg, 1990 (1)$\dagger$</td>
<td>0.6 (0.4–1.0)</td>
<td>0.68 (0.58–0.80)</td>
<td>0.69 (0.58–0.82)</td>
<td>Age, sex</td>
</tr>
<tr>
<td>Pooled estimates</td>
<td>0.61 (0.55–0.67)</td>
<td>0.68 (0.58–0.80)</td>
<td>0.69 (0.58–0.82)</td>
<td></td>
</tr>
</tbody>
</table>

* Blank cells appear when the specific exposure–disease association was not evaluated in that particular study. CI = confidence interval; RR = relative risk; SES = socioeconomic status.

† Studies included in final pooled analysis. The remaining studies were not included because of insufficiently detailed exposure definition (8) or because the data (2–4) were also part of pooled analysis [reference (5)].
The atopic diseases that were included in this analysis encompass a range of airway, cutaneous, gastrointestinal, and vascular pathologies that were self-reported as eczema, asthma, or allergy. In the context of such variable definitions of atopic disease, it is striking that the associations of these various pathologies with risk of glioma were strong and consistent across studies. Furthermore, these results are consistent with the finding that IgE, which is a biomarker of atopic allergy whose measurement is unaffected by individual recall and reporting, was also inversely associated with glioma. A case–control study that included 228 subjects with available serum samples reported an odds ratio of 0.37 (95% CI = 0.22 to 0.64) comparing those with high total serum IgE levels to those with normal levels (14).

Despite their variety, the different manifestations of atop are all characterized by the production of Th2 cytokines, including IL-4 and IL-13. Single-nucleotide polymorphisms in the gene coding for the α-chain of the IL-4 receptor, which is common to both the IL-4 and IL-13 signaling pathways, and in the gene for IL-13 itself have been associated with an increased risk of asthma (22–24). Intriguingly, these same polymorphisms were also inversely associated with glioma susceptibility in one study (13). It is possible that Th2 cytokines may help protect against glioma through their regulation of humoral immunity, including the production of B-cell antibodies. Although the brain is regarded as an “immunologically privileged” site (25), peritumor inflammation alters the properties of the blood–brain barrier and allows infiltration by cells of the peripheral immune system (26,27). Thus, in addition to humoral immunity, cell-mediated immunity may also be involved in the response to gliomas (28).

Considerable experimental evidence, including evidence from rodent models, supports a role for IL-4 in the immune response to gliomas. For example, immunization of glioma-bearing rats with tumor cells overexpressing IL-4 led to rejection of an otherwise fatal progressive glioma (11). Likewise, neural progenitor cells engineered to overexpress IL-4 produced regression of induced gliomas in both mice and rats (29). Gliomas are known to express transforming growth factor β (30), and this cytokine may in fact function in synergy with IL-4 to drive local Th1 responses (31). Indeed, the protective responses seen in rats immunized with IL-4–overexpressing gliomas were associated with the production of high levels of the Th1 effector cytokine interferon gamma by tumor-infiltrating CD4+ T cells (32). Furthermore, it is possible that IL-4 and other Th2 cytokines have protective actions through a range of individual pleiotropic effects that are not directly related to the Th1/Th2 paradigm, which sees Th1 and Th2 cytokines as driving opposing—at times antagonistic—immunologic pathways. Such effects might include the suppression of angiogenesis (33). In addition, IL-4 has been shown to inhibit DNA synthesis in low-grade astrocytoma cell lines but not in more aggressive tumor cell lines (34), and similar results have been demonstrated for IL-13 (35), raising the possibility that these cytokines may act to disrupt tumor progression rather than initiation.

If Th1 responses are also important for prevention or rejection of gliomas and the apparent protection is related to increased immune reactivity rather than to a Th1/Th2 dichotomy, then the apparent protection from glioma associated with atopy should also be seen with other immunopathologies, including some autoimmune conditions that are regarded as Th1 in nature, such as type 1 diabetes or multiple sclerosis. In this regard, the study of Brenner et al. (7) is informative in that it showed an inverse association between a history of either autoimmune or atopy with glioma that was strongest in those reporting a history of both (7). Future studies seeking to clarify the nature of the relationship between immune conditions that are regarded as Th1 in nature, such as type 1 diabetes or multiple sclerosis. In this regard, the study of Brenner et al. (7) is informative in that it showed an inverse association between a history of either autoimmune or atopy with glioma that was strongest in those reporting a history of both (7). Future studies seeking to clarify the nature of the relationship between immune

Discussion
The results of this meta-analysis suggest an inverse association between atopy and glioma; specifically, the risk of glioma was 40% lower among those with a history of allergy than those with no such history, 30% lower among those with a history of eczema, and 30% lower among those with a history of asthma. This inverse association with allergy persisted when the analysis was restricted to studies without proxy responders and when accounting for publication bias. No overall association was noted for allergy and meningioma, although a smaller number of cases of this disease were available.

The atopic diseases that were included in this analysis encompass a range of airway, cutaneous, gastrointestinal, and vascular pathologies that were self-reported as eczema, asthma, or allergy. In the context of such variable definitions of atopic disease, it is striking that the associations of these various pathologies with risk of glioma were strong and consistent across studies.
status and glioma should also address T_{h}1-mediated pathologies, as well as the more thoroughly studied T_{h}2 responses.

Meningioma is a disease with distinct pathology and progression to that of glioma. The dissimilar results in relation to atopic disease could therefore be due to differences in tumor etiology. If the inverse association noted for atopy is a function of elevated immune reactivity acting to limit tumor progression rather than incidence, we might expect an inverse association between atopy and all brain tumors, especially among more rapidly progressive cancers that might trigger stronger inflammatory responses. The findings of Schwartzbaum et al. (8) suggest a stronger inverse association between allergy status and high-grade, but not low-grade, glioma and hence support this hypothesis. In this context, the slowly progressive nature of meningioma may elicit a milder immune response, explaining the weaker association observed here. Although the few studies on meningioma associations with atopy showed heterogeneous results, we identified one study that contributed to most of the heterogeneity. Exposure assessment may have been less accurate in this study because it was the only investigation to measure atopy using a single question. Interestingly, when this study was excluded the pooled estimate for the remaining homogeneous studies became inverse and statistically significant. Moreover, a history of autoimmunity has been associated with a lower risk of meningioma as well as of glioma (7), emphasizing the potential importance of a vigorous immune response in protection from any intracranial tumor. However, more studies are needed to confirm this hypothesis.

Despite the intriguing findings of this meta-analysis, it has several important limitations. One is that brain tumors are rare and glioma is a rapidly progressive disease, making it difficult to obtain high-quality information in epidemiologic investigation. To date, most of the information on this topic comes from case-control studies, which permit larger number of cases than prospective cohorts of rare diseases but are limited by retrospective ascertainment of exposure and do not provide a clear definition of the temporal relation between exposure and disease. The possibility of selection bias was evaluated by considering the selection of controls and control response rates (range = 43%–87% in included studies; data not shown). Control selection was generally appropriate in all studies included, making selection bias an unlikely explanation for the consistent inverse association.

In addition, measurement error associated with exposure is of particular concern when using self-reported measures. Many studies included in our meta-analysis tried to elicit a history of physician-diagnosed or medically treated atopy in an attempt to reduce exposure misclassification (1,6–9,13). The reliability of self-reported measures of allergies was addressed in some studies, which quoted similar rates of disease in the control subjects or underlying cohort and in the general population (6,8). Moreover, the validity of self-reported asthma measures from questionnaires compared with the gold standard of clinical diagnosis is reasonably high; average sensitivity is 68%, and average specificity is 94% (36). Therefore, measurement error is less problematic with this subtype of atopic disease.

A further difficulty in drawing causal interpretations from observational data occurs if the temporal order of exposure preceding outcome is not clearly defined and reverse causation cannot be excluded. Brain tumors are known to depress immune function (26,37), and the latency period of glioma is not fully established. Therefore, it is possible that both IgE levels and allergic reactions reported by patients with glioma are influenced by subclinical cancer. Some studies have addressed this issue by obtaining information about allergy many years preceding glioma diagnosis (2–5,13) and by collecting data on overall duration, latency, and age of onset (5–7,9). However, because inverse associations were also observed when allergies developed at an early age or when they were present many years before brain cancer diagnosis (5–9), reverse causation is unlikely to be responsible for the overall findings.

We also considered publication bias and systematic differences due to reporting by proxy as potential alternative explanations for these findings. Our sensitivity analyses and funnel plot imply that these biases are unlikely to fully account for the strong and consistent associations observed.

Future prospective studies may be able to clarify the temporality of this relationship by confirming that atopic disease precedes cancer incidence. However, the lack of adequate data on history and timing of atop conditions in most cohort questionnaires limits exposure assessment. Instead, blood markers of atopy, including serum IgE collected before diagnosis, may be a more appropriate way to examine this association. Moreover, information from multiple cohort studies will likely need to be pooled to allow for adequate numbers of cases.

In summary, a history of atopic disease is inversely associated with risk of glioma. These results are consistent across many geographic settings, study designs, and different atopic diseases and may reflect a protective effect of the immunologic milieu associated with atopic allergy on tumor growth. Furthermore, some data exist to support the biologically plausible proposition that the inverse association of atopy with glioma reflects a broader association between heightened immunity and intracranial tumors. Methodologic limitations are unlikely to explain the full magnitude of the observed effect, but there remains a need for further prospective studies that can more clearly evaluate the temporal relationship between atopy and brain tumors.

References
