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Asthma and Risk of Glioma: A Population-Based Case-Control Study

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Abstract (257/300 words)

Objectives: Literature suggests an inconsistent, but largely inverse, association between asthma and risk of glioma, which is primarily due to methodological inconsistency in sampling frame and ascertainment of asthma and/or glioma diagnosis. Objective of the study was to clarify the association between asthma and risk of glioma by minimizing methodological biases.

Design: A population-based case-control study

Setting: General population in Olmsted County, Minnesota, US

Participants: All eligible biopsy-proven incident glioma cases (1995-2014) and two sets of controls among residents matched to age and sex (1st set: community controls without glioma; 2nd set: MRI-negative controls from the same community).

Methods: The predetermined asthma criteria via medical record review were applied to ascertain asthma status of cases and controls. History of asthma prior to index date was compared between glioma cases and their matched controls using conditional logistic regression models.

Results: We enrolled 135 glioma cases (median age at index date: 53 years) and 270 controls. Of the cases, 21 had a history of asthma (16%), compared to 17 of community controls (13%) and 36 of MRI controls (27%) [OR (95%CI): 1.29 (0.64-2.59), p=0.48, for community control versus 0.48 (0.26-0.91), p=0.03, for MRI control]. With MRI controls, inverse association between asthma and risk of glioma remained after adjusting for smoking and socioeconomic status but was not statistically significant [OR (95%CI): 0.55 (0.28-1.08), p=0.08].

Conclusions: While differential detection might account for the association between asthma and risk of glioma, asthma may pose a protective effect on risk of glioma. Our study results need to be replicated by a larger study.

Key Words (3-5 words): glioma, asthma, epidemiology, sampling, allergy

Strengths and limitations of this study:

1. This is a population-based case-control study performed in a self-contained community to address selection bias.
2. Predetermined asthma criteria (exposure) and biopsy-proven glioma case ascertainment (outcome) were used along with two different sets of controls to mitigate detection bias.
3. Laboratory data and lung function testing results not included in the study results.
4. Our study includes a small number of glioma cases with study setting mostly consisting of Caucasian patients (i.e., limited generalizability)

Data sharing statement: No additional data available.

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INTRODUCTION

Glioma is the most common primary intracranial malignant tumor (1). Approximately, 17,600 new cases of gliomas are diagnosed per year with a 5-year survival rate of 27% (2). Although treatment options have improved with better understanding of the molecular biology of these tumors, malignant glioma remains incurable with largely unknown etiology.(3).

Recently, germline variants highly associated with glioma were shown to interact with asthma and allergy risk, indicating an immunological involvement in the risk of glioma (4, 5). Single nucleotide polymorphisms related with glioma have also been studied for an association with atopic dermatitis (6). Several studies describe the association between atopy or asthma and developments of gliomas (7, 8) but the results have been inconsistent (9, 10). eTable 1 summarizes literature regarding asthma (or atopic conditions) and risk of glioma as well as their study designs.

An inverse association between history of allergy and risk of glioma was found in the majority of studies (11). These studies have methodological limitations. For example, some studies were cross-sectional ones obscuring temporality between asthma (exposure) and risk of glioma (outcome)(12, 13). Some studies allowed dissimilarity between cases (referred glioma cases identified from a tertiary center, cases identified by ICD codes) and controls (community population) in terms of source population (susceptibility bias and detection bias) (14). Many studies are based on self-reported allergic conditions, which can be influenced by the rapidly debilitating nature of glioma

causing cognitive and memory impairment leading to misclassification of asthma.(4, 5, 12, 15)

To address these limitations in assessing the relationship between asthma and risk of glioma, we designed this study as a population-based case-control study that enrolled all eligible biopsy-proven incident glioma cases and two sets of matched-controls from the community population i.e., (1) community controls who do not have history of glioma, and (2) MRI-controls with negative test results. This study design allows examining a potential detection bias. In addition, we utilized predetermined asthma criteria (delineated in Table 1) and performed a comprehensive medical record review to objectively ascertain the asthma status.

METHODS:

Study Setting

Olmsted County, southeastern Minnesota is an excellent setting to conduct a population-based epidemiologic study because medical care is virtually self-contained within the community. When patients register with any health care providers in the community, they or their parents/legal guardian are asked to grant authorization of use of their medical records for research. Authorization is granted by over 95% of all individuals. Comprehensive medical records research at Olmsted County is made possible through the Rochester Epidemiology Project (REP), which has been continuously funded by NIH and maintained since 1966.(16) The REP database consists of all medical records from two major medical centers (Mayo Clinic Rochester and Olmsted Medical Center) and their affiliated hospitals. Only those individuals with

current research authorization were included in this study. The population demographics of Olmsted County and of those included the REP database have been previously described.(16)

Study Design and Study Subjects:

A retrospective population-based case-control design was employed. Patients diagnosed with glioma (cases) during1995-2014 and their two matched controls (see Case Ascertainment and Selection of Controls) were identified from the REP database representing Olmsted County, MN residents. Asthma status prior to index date of cases and their matched controls was ascertained by predetermined asthma criteria and its frequency was compared between cases and controls (each control group and both control groups separately). The Olmsted Medical Center (OMC) and Mayo Clinic Institutional Review Boards approved this study.

Patient and public involvement

No patients or the public were involved in the study protocol design, the specific aims or the research questions, and the plans for the design or implementation of the current study. No patients or the public were involved in the interpretation of the results of the study or preparation of the manuscript. There are no plans to disseminate the results of the research to study participants.

Case Ascertainment

All Olmsted County residents who developed glioma during the study period of January 1st, 1995, to December 31st, 2014, were identified from the Mayo Clinic Tumor Registry and the REP using medical index search codes. The medical index search codes used for this study include HICDA (Mayo's modified version of the Hospital Adaptation of the Internal Classification of Diseases, used at Mayo since 1975) and ICD-9 codes. Each preliminary case was reviewed to ascertain cases that met the enrollment criteria, including 1) Olmsted County residency at the index date and one year prior to index date, with 2) research authorization, and 3) pathology confirmed glioma cases [e.g., astrocytoma, oligodendroglioma, gliomatosis cerebri, mixed gliomas (oligoastrocytoma), and glioblastoma] of brain and spinal cord. The index date was defined as the date of glioma diagnosis by pathology reporting. World Health Organization (WHO) classification of primary brain tumors according to histology and grade was applied (i.e., Grade I, II-III, Grade IV).(17)

The exclusion criteria included: 1) non-Olmsted County residents at or one year prior to index date, 2) individuals without research authorization, 3) insufficient medical records for determining case and exposure status, 4) non-glioma tumor types (e.g., recurrent glioma, metastatic brain tumor, ependymoma, and non-glial brain tumor [e.g., meningioma]), 5) glioma-related hereditary syndrome (e.g., tuberous sclerosis, neurofibromatosis types 1 and 2), 6) absence of a tissue diagnosis, and 7) clinical conditions making asthma ascertainment difficult (see Table 1).

Selection of Controls

Two controls per case, matched based upon birth year, sex, and registration year, to ensure similar exposure to healthcare between cases and controls, were identified in the REP database. The first cohort of controls included subjects selected from the population in Olmsted County who did not have any history of glioma by HICDA and ICD-9 codes for initial screening confirmed by medical record review ("community control"). The second controls were subjects who had undergone brain or neck imaging, identified by CPT codes completed within one year of their corresponding case diagnosis, who had normal findings ("MRI control"). The index date for control was same as the one of their corresponding case. Controls were held to the same enrollment and exclusion criteria as cases. Reasons for MRI imaging among the MRI controls were reviewed and reported (eTable 2).

Asthma Ascertainment

We determined asthma status prior to the index date for both cases and controls according to predetermined asthma criteria (PAC) outlined in Table 1. Both definite and probable asthma statuses were considered as asthma as most probable asthma became definite asthma over time(18). This asthma criteria was originally developed by Drs. John Yunginger and Charles Reed(18) and has shown excellent construct validity and reliability (0.72-0.92) of the criteria (18-21). The onset date of asthma (asthma inception date) by PAC, was defined as the earliest constellation of symptoms found in the medical record that met the PAC.

Active (or current) asthma was defined as the presence of any asthma-related events, including asthma symptoms (e.g., wheezing, night cough, dyspnea), use of asthma medications (e.g. short-acting beta agonists, inhaled corticosteroids, leukotriene

inhibitors), and/or outpatient, inpatient or emergency department (ED) visits for asthma within 12 months of the index date. Poorly controlled asthma was defined as the presence of any asthma symptoms, use of systemic corticosteroid for asthma symptoms, or unscheduled visits for asthma, including ED or hospitalization for asthma, within six months prior to index date (22).

For those patients with an electronic medical record (EMR) at Mayo Clinic available since 1997, we used a natural language processing (NLP) algorithm to determine PAC (NLP-PAC; automatic chart review for EMR by computer).This was developed and validated for automatic chart review for determining PAC by computer and the details have been recently reported (23). Briefly, validation performance of NLP-PAC was promising with 97%, 95%, 90%, and 98% for sensitivity, specificity, positive predictive value, and negative predictive value of NLP algorithm against manual chart review. This NLP-PAC algorithm has been externally validated by assessing validity in a different study setting (Sioux Falls, South Dakota) (24)

Other variables

Demographics including sex, age, race and clinical characteristics including family history of asthma, and a physician diagnosis of other atopic conditions (eczema and allergic rhinitis) were reported. A family history of asthma, smoking status within 3 months prior to index date (second-hand smoking included for pediatric population), pneumococcal and seasonal influenza vaccine status as a surrogate marker for access to health care service, co-morbid conditions (history of epilepsy, stroke or transient ischemic attack (TIA), rheumatoid arthritis, lupus erythematosus, multiple sclerosis, and

diabetes) were collected by abstractors. Factors related to socioeconomic status (SES) were measured using an individual-level housing-based socioeconomic status measure we developed and validated, called HOUSES. (25, 26) This data was formulated as standardized z-scores based on the address information at index date using real property data (i.e. value, size, number of bedrooms and bathrooms) after geocoding.(25) Higher HOUSES values equate to higher socioeconomic status.

Statistical Analysis

We summarized the characteristics of cases and controls using descriptive statistics. We performed matched analysis with conditional logistic regression to determine the association between asthma status and risk of glioma. Conditional logistic regression models were used to estimate odds ratios (OR) and their corresponding 95% confidence intervals (95% CIs). We used the Greenland entry criteria for multivariable analysis ($p<0.20$ based on univariate analysis)(27). We also looked at subgroups (i.e., stratified by tumor grade) differences between groups although no formal comparisons were made because of the small sample sizes. All analyses were performed using SAS statistical software package (Ver 9.4; SAS Institute, Inc., Cary, NC).

RESULTS

Study subjects

A total of 567 patients were found in the Mayo Clinic Tumor Registry or the Rochester Epidemiology Project (REP) with a diagnosis code for glioma. Of these, 432 were

excluded for not meeting the inclusion criteria or meeting the exclusion criteria, with 135 as our final cases (eTable 3).

The sociodemographic characteristics are summarized in Table 2. Overall, cases and controls (MRI and community) were similar except for smoking exposure. Glioma cases were less likely to have a history of smoking exposure (OR [95% CI]: 0.6 [0.4-1.0]). When we compared each control set (i.e., community controls and MRI controls) with cases in terms of socioeconomic status (HOUSES) and access to health care (seasonal flu vaccine and PPSV23), we found MRI controls were more similar to cases than population controls. This suggests that MRI controls may be more representative of the source population to compare against the glioma cases in this study. Reasons for MRI imaging among the MRI control group are summarized in eTable 2, and these reasons seem to unlikely affect our study results. With regard to SES, median HOUSES, given as a z score, among cases was -0.2 (IQR: -1.7-2.3) which tended to be higher than MRI controls (median [IQR]: -0.8 [-2.6-2.3]), although not significant (P=0.17).

Comparison of prevalence of asthma between glioma cases and controls

In the combined control set, there was no association between asthma and risk of glioma (OR [95%CI]: 0.74 [0.41-1.31], P=.30). However, 21 (16%) of the 135 cases had asthma, whereas 36 (27%) of the 135 MRI controls and 17 (13%) of the 135 community controls had asthma (OR [95%CI]: 0.48 [0.26-0.91]; p=0.03 for MRI controls and OR [95%CI]: 1.28 [0.64-2.59]; p=0.48 for community controls; see Table 3).

Active asthma (OR 0.40, 0.17-0.93) was associated with a stronger inverse association with glioma risk compared to inactive asthma (0.58, 0.26-1.28) when using non-asthmatic group as the reference group. Poorly controlled asthma (0.1, 0.02-1.1) showed similar effect, but not reached statistical significance. We assessed the association of asthma status with cases (vs. MRI controls) after adjusting for smoking exposure and HOUSES, and found asthma was still protective of glioma but only approached, but did not reach, statistical significance (OR [95%CI]: 0.55 [0.28, 1.08]; p =0.08) (Table 4). When we stratified cases by WHO grade (I [n=19], II-III [n=40], and IV [n=76]), glioma cases were less likely to have a history of asthma compared to MRI controls in all grades (16% [cases] vs. 47% (0.21, 0.05-0.96) [MRI controls], 18% vs. 30% (0.50, 0.17-1.43), 15% vs. 20% (0.69, 0.29-1.62)for Grade I, II-III, and IV, respectively)

Comparison of prevalence of other comorbidities between glioma cases and controls

Neither other atopic conditions (e.g., eczema, allergic rhinitis) nor family history of asthma was associated with risk of glioma in either set of controls (Table 3). Stroke or TIA was significantly associated with risk of glioma in comparison with either control group, but diabetes was not. Other comorbidities assessed such as epilepsy, rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis were very rare in our cohort and were not analyzed.

DISCUSSION

In this study, using two different control sets, while asthma tends to be inversely associated with the risk of glioma based on MRI controls, such association was not supported in community controls. As MRI controls were more similar to cases (than

community controls), our study results may uphold previous study results supporting an inverse association between asthma and risk of glioma. At the same time, these differential results depending on controls account for inconsistent results and their source (selection bias).

Patients with asthma may seek health care more often than those without asthma, resulting in an increased chance of detecting glioma (and other health outcomes) (detection bias),(28) and we tried to reduce detection bias by enrolling MRI-proven controls (similar chance for detecting glioma between cases and controls). If detection bias occurred to our, one would expect an increased detection of asthma among MRI controls (e.g., a marker for care seeking) leading to a null association and a lower detection of asthma among community controls resulting in a positive association between asthma and risk of glioma. . However, our study results were contrary to this anticipation (i.e., an inverse association between asthma and the risk of glioma using MRI controls and no association in community controls), and thus, MRI controls might negate potential detection bias. In addition, as MRI controls are more similar to glioma cases in terms of clinical and socioeconomic variables, we believe MRI controls may be more representative for a source population from who glioma cases were drawn.

To minimize misclassification bias for asthma status from self-report or ICD codes, we utilized an objective method for asthma ascertainment by applying predetermined asthma criteria (PAC) through comprehensive medical record review. Apart from the association between asthma status and risk of glioma, in the analysis using MRI controls, active asthma showed a more protective effect than inactive asthma and

similarly poorly controlled asthma posed a more protective effect than not-poorly controlled asthma, although it did not reach statistically significance. Therefore, overall, our results on an inverse association between asthma and the risk of glioma based on MRI controls might uphold prior observations supporting such inverse associations.

The relationship between asthma and risk of malignancy in general varies depending on the type of malignancy. For example, asthma has been shown to increase the risk for lung cancer while inverse association of asthma with multiple tumors has been reported including pancreatic or stomach cancer, acute lymphoblastic leukemia, gliomas, non-Hodgkin's lymphoma, and even colorectal cancer(29, 30). Hyperactive immune systems in patients with allergic disorders could cause a lower incidence of cancers(31). In fact, presence of any allergic disorder (eczema, allergic rhinitis or asthma) in studies with twins or similar genetic and environmental factors have demonstrated lower association with gliomas(32). However, in our study, atopic conditions other than asthma were not associated with the risk of glioma. It is uncertain whether this lack of association is due to a methodological issue as these conditions were determined by ICD codes instead of predetermined criteria as used in asthma. Along these lines, a family history of asthma as a marker for shared genetics or environment (33) was not associated with the risk of glioma in our study which is consistent with the literature (34, 35).

The mechanisms underlying the potential inverse association is unknown. It is important to determine which one (asthma vs. its associated risk factors [i.e., confounders]) is responsible for this observed potential inverse association. As our

study is epidemiological and focused on clarification of inconsistent results of the literature, this study question needs to be addressed in the future.. Literature suggests that immunoglobulin E plays a role in reducing the risk of cancers and use of IgE monoclonal antibodies for the passive immunotherapy in murine models has been found to kill tumor cells in multiple previous studies via antibody dependent cellular toxicity(36),(37). Along these lines, cytokines associated with Th2-immune responses have shown anti-tumor activity(38). For example, IL-5 which is a cytokine produced by lymphoid cells has been found to recruit eosinophils and create a microenvironment that prevents tumor formation in the lung. However, whether this type of anti-tumor activity is applicable to glioma needs to be studied. Though the underlying mechanisms remain poorly understood, our work clarified the inconsistency of the literature on the association between asthma and risk of glioma and provides an insight into a potential inverse association between asthma and risk of glioma.

Our study also has some inherent limitations as a retrospective study. We did not include laboratory or lung function data to measure Th2 immune responses or other inflammatory responses, which might help us to discern the study results. Our study was limited due to a small number of glioma cases even if our study included all eligible population-based cases. These study results need to be replicated with a larger number of glioma cases in future studies. As our study setting mostly consists of Caucasian patients, generalizability of our study results to other settings or ethnic groups needs to be cautious. Our study also has important strengths. The study setting has unique advantages, including a self-contained health care environment and a medical record linkage system. This is also a population-based study design, which minimizes a

selection bias. In addition, as we only included incident cases of glioma and determined index date of asthma as well, we were able to assess temporality on the relationship between asthma and risk of glioma. We used two sets of controls to mitigate or assess detection bias as described above. In addition, ascertainment of asthma status by using the PAC was performed independent of asthma status by a physician diagnosis of asthma, which minimized an observational bias.

Conclusion

Our study results suggest that asthma may pose a protective effect on the risk of developing glioma but the results need to be replicated in a larger study. In addition, our study results clarify the rationale for the inconsistent results on the relationship between asthma and risk of glioma.

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Table 1. Predetermined Asthma Criteria

Patients were considered to have *definite* asthma if a physician had made a diagnosis of asthma and/or if each of the following three conditions were present, and they were considered to have *probable* asthma if only the first two conditions were present:

1. History of cough with wheezing, and/or dyspnea, OR history of cough and/or dyspnea plus wheezing on examination,
2. Substantial variability in symptoms from time to time or periods of weeks or more when symptoms were absent, and
3. Two or more of the following:
   - Sleep disturbance by nocturnal cough and wheeze
   - Nonsmoker (14 years or older)
   - Nasal polyps
   - Blood eosinophilia higher than 300/uL
   - Positive wheal and flare skin tests OR elevated serum IgE
   - History of hay fever or infantile eczema OR cough, dyspnea, and wheezing regularly on exposure to an antigen
   - Pulmonary function tests showing one FEV_1 or FVC less than 70% predicted and another with at least 20% improvement to an FEV_1 of higher than70% predicted OR methacholine challenge test showing 20% or greater decrease in FEV_1
   - Favorable clinical response to bronchodilator

Patients were excluded from the study if any of these conditions were present:

- Pulmonary function tests that showed FEV_1 to be consistently below 50% predicted or diminished diffusion capacity
- Tracheobronchial foreign body at or about the incidence date
- Hypogammaglobulinemia (IgG less than 2.0 mg/mL) or other immunodeficiency disorder
- Wheezing occurring only in response to anesthesia or medications

The following diseases excluded the patient from study if they occurred before the incidence date:

- Bullous emphysema or pulmonary fibrosis on chest radiograph
- PiZZ $alpha_1$-antitrypsin
- Cystic fibrosis
- Other major chest disease such as juvenile kyphoscoliosis or bronchiectasis

FVC forced vital capacity; FEV1, forced expiratory volume in 1 sec.

Table 2. Sociodemographic characteristics of study subjects

	Cases (n=135)	All controls (n=270)	OR (95%CI) for all controls	MRI controls (n=135)	OR (95%CI) for MRI controls	Community controls (n=135)	OR (95%CI) for Community controls
Age, years, median (IQR)	53 (32, 68)	53 (32, 68)	-	53 (32, 68)	-	53 (32, 68)	-
Female, n (%)	61 (45)	122 (45)	-	61 (45)	-	61 (45)	-
White, n (%)	126 (93)	242 (90)	1.7 (0.7-3.7)	123 (91)	1.4 (0.6-3.4)	119 (88)	2.2 (0.8-5.7)
Education							
Missing	20	13		331 (23)	-	10	
High School or less	31 (27)	78 (30)	0.7 (0.4-1.3)	37 (28)	1.5 (0.6-3.3)	47 (38)	0.3 (0.1-0.7)**
Some college	36 (31)	70 (27)	0.8 (0.5-1.5)	24 (18)	1.0 (0.5-1.8)	33 (26)	0.5 (0.2-1.1)
College completion	13 (11)	47 (18)	0.4 (0.2-1.0)**	40 (30)	0.6 (0.2-1.3)	23 (18)	0.3 (0.1-0.8)**
Graduate education	35 (30)	62 (24)	(ref)		(ref)	22 (18)	(ref)
HOUSES, Z (median, IQR)	-0.2 (-1.7, 2.3)	-0.7 (-2.7,1.9)		-0.8 (-2.6,2.3)		-0.6 (-2.7,1.8)	
HOUSES, n (%)							
Missing	526 (20)	1271 (28)	-	6	-	6	-
Q1 (lowest SES)	33 (25)	64 (25)	0.6 (0.3-1.1)	38 (30)	0.5 (0.3-1.2)	33 (26)	0.6 (0.3-1.3)
Q2	35 (27)	62 (24)	0.9 (0.5-1.6)	30 (23)	0.9 (0.5-1.8)	34 (26)	0.8 (0.4-1.7)
Q3	36 (28)	61 (24)	0.9 (0.5-1.7)	26 (20)	1.1 (0.6-2.1)	36 (28	0.8 (0.4-1.5)
Q4			(ref)	35 (27)	(ref)	26 (20)	(ref)
Seasonal flu vaccine, n (%)	63 (47)	112 (42)	1.3 (0.8-2.0)	62 (46)	1.0 (0.6-1.7)	50 (37)	1.7 (1.0-3.1)*
PPSV23[a], n (%)	33 (24)	69 (26)	0.9 (0.5-1.7)	39 (29)	0.7 (0.3-1.4)	30 (22)	1.2 (0.6-2.5)
Smoking exposure, n (%)							
Undocumented	4 (3)	15 (6)	0.5 (0.1-1.4)	3 (2)	1.1 (0.2-5.1)	12 (9)	0.2 (0.1-0.9)**
Yes	48 (36)	119 (44)	0.6 (0.4-1.0)*	67 (50)	0.5 (0.3-0.9)**	52 (39)	0.8 (0.4-1.3)
No	83 (62)	136 (50)	(ref)	65 (48)	(ref)	71 (53)	(ref)

*p<0.1, **p<0.05 ; [a] Pneumococcal polysaccharide vaccine 23 Percentages may not add up to 100 due to rounding Odds ratios are not presented for matching variables

Table 3. Association of asthma and other atopic conditions with cases compared to controls

	Cases (n=135)	All controls (n=270)	OR (95%CI) for all controls	MRI controls (n=135)	OR (95%CI) for MRI controls	Community controls (n=135)	OR (95%CI) for Community controls
Asthma PAC[a], n (%)	21 (16)	53 (20)	0.7 (0.4-1.3)	36 (27)	0.5 (0.3-0.9)**	17 (13)	1.3 (0.6-2.6)
Asthma activity, n (%)							
No asthma	114 (84)	217 (80)	(ref)	99 (73)	(ref)	118 (87)	(ref)
Inactive asthma	11 (8)	24 (9)	0.9 (0.4-1.8)	16 (12)	0.6 (0.3-1.3)	8 (6)	1.4 (0.5-3.8)
Active asthma	10 (7)	29 (11)	0.6 (0.3-1.4)	20 (15)	0.4 (0.2-0.9)**	9 (7)	1.1 (0.4-3.2)
Asthma control, n (%)							
No asthma	114 (84)	217 (80)	(ref)	99 (73)	(ref)	118 (87)	(ref)
Not poorly controlled asthma	19 (14)	43 (16)	0.9 (0.5-1.6)	29 (21)	0.6 (0.3-1.1)	14 (10)	1.5 (0.7-3.0)
Poorly controlled asthma	1 (1)	10 (4)	0.2 (0.03-1.5)	7 (5)	0.1 (0.02-1.1)*	3 (2)	0.3 (0.04-3.5)
Eczema, n (%)	11 (8)	24 (9)	0.9 (0.4-1.9)	17 (13)	0.6 (0.3-1.4)	7 (5)	1.7 (0.6-4.6)
Allergic rhinitis, n (%)	28 (21)	53 (20)	1.1 (0.6-1.8)	30 (22)	1.0 (0.5-1.6)	23 (17)	1.3 (0.7-2.4)
Family history of asthma, n (%)				36 (27)			
Undocumented	34 (25)	87 (32)	0.5 (0.2-1.0)**	15 (11)	0.8 (0.4-1.8)	51 (38)	0.4 (0.2- 0.9)**
Yes	12 (9)	22 (8)	1.0 (0.5-2.1)	84 (62)	0.8 (0.3-1.7)	7 (5)	1.5 (0.5-4.1)
No	89 (66)	161 (60)	(ref)		(ref)	77 (57)	(ref)

*p<0.1, **p<0.05 ; [a] Predetermined asthma criteria Percentages may not add up to 100 due to rounding Odds ratios are not presented for matching variables

Table 4. Multivariable analysis: Cases vs. MRI Controls

Variable	Comparison	Adj. Odds Ratio	95% CI	P-value
Asthma PAC	Yes. Vs. No	0.55	0.28 -1.08	0.08
Smoking History	Yes vs. No	0.51	0.28 - 0.92	0.08
	Unknown vs. No	0.83	0.16 - 4.74	
HOUSES in quartile (4th: highest SES)	1st vs. 4th	0.61	0.28 - 1.36	0.46
	2nd vs. 4th	0.97	0.48 - 1.96	
	3rd vs. 4th	1.09	0.55 - 2.15	

eTable 1. Description of epidemiologic studies on asthma or atopic conditions and risk of glioma

Authors	Design	Study subjects and source population	Definition of glioma	Independent variable	Results	Conclusion
A. Inverse association						
Schlehofer, Europe, 2011(39)	Nested case-control study	Case:275 Control: 963	Histologically proven cases of glioma	IgE ≥0.35 kUA/L	1. OR 0.73 (0.51-1.06) overall, 0.53 (0.30-0.95) in women 2. P for trend=0.04 (the lowest OR observed in sera with the highest IgE levels)	A reduced risk for glioma with allergic sensitization
Wigertz, Europe, 2007(15)	5 case-control studies (5 countries in Europe)	Case:1527 Control:3309	ICD codes	MD diagnosed atopic conditions (asthma, hay fever, eczema, food allergy)	For each atopic condition, OR 0.65~0.66 (p<0.05 in all) (current rather than past, except in asthma)	A reduced risk for glioma primarily with current allergic conditions
Brenner, USA, 2002 (12)	Case-control study	Case: 489 Control: 799	Histologically proven with ICD confirmation	MD diagnosed allergic conditions (asthma, hay fever, eczema)	1. Any allergy a. Low-grade glioma OR 0.72 (0.47-1.10) b. High-grade glioma OR 0.67 (0.5-0.89) 2. Asthma, OR 0.63 (0.43-0.92) 3. Hay fever, OR 0.97 (0.69-1.37) 4. Eczema, OR 0.76 (0.45-1.27)	Reduced risk for glioma in those with asthma or any allergy
Wiemels, USA, 2009 (8)	Case-control study	Case: 535 Controls: 532	Histologically confirmed glioma	In-person interviews and IgE measurement	Glioma patients reported significantly fewer allergies than controls (OR = 0.50, 95% CI: 0.36–0.70)	The study described an inverse association of self-reported allergy and glioma
Schwartzbaum, USA, 2003(13)	Cohort studies	Questionnaire Respondents: Cohort 1: 14,535 Cohort 2: 29,573 Cohort 3: 52,067	Swedish mortality and cancer registry	Self-reported allergic diseases	Allergies are inversely associated with glioma risk in Cohort I (Hazard ratio [HR] 0.45; 95% CI 0.19 –1.07) and among high grade (III and IV, HR 0.45; 95% CI 0.11–1.92) but not low grade (I and II, HR 2.60; 95% CI 0.86 –7.81) gliomas in Cohort II. In Cohort III, immune-related discharge diagnoses are also inversely associated with glioma (HR 0.46; 95% CI 0.14 –1.49).	There is no strong evidence against (and some for) the hypothesis that allergies reduce glioma risk.
B. No association						
Calboli, USA, 2011(40)	4 Cohort studies	Case: 169 Controls: 520	Glioma cases from medical records, death certificates or pathology proven	Self-reported history of asthma IgE measurement: 25-100kU/L: Borderline >100kU/l: Elevated	There was an inverse association of borderline statistical significance (P = .07) for total IgE levels higher than clinically normal levels and risk of glioma (total IgE ≥25 vs<25 kU/L, odds ratio [OR] = 0.72, 95% CI = 0.51 to 1.04)	No statistically significant associations between allergy measurements and risk of glioma.
Disney Hogg, UK, 2018 (6)	Meta-analysis of Genome wide association studies	Cases: 12,488 Controls: 18169	Genome wide association studies dataset for glioma	Single nucleotide polymorphisms (SNPs) associated with atopic dermatitis, asthma and hay fever, IgE levels, and self-reported allergy	An inverse relationship between atopic dermatitis and glioma risk was found by inverse-variance weighting (OR 0.96, 95% confidence interval (CI) 0.93–1.00, P = 0.041) and maximum likelihood estimation (OR 0.96, 95% CI 0.94–0.99, P = 0.003),	Study results provide evidence for a causal protective effect of atopic dermatitis with GBM tumors, but do not provide evidence that asthma and hay fever, raised IgE levels, or self-reported allergy is protective against

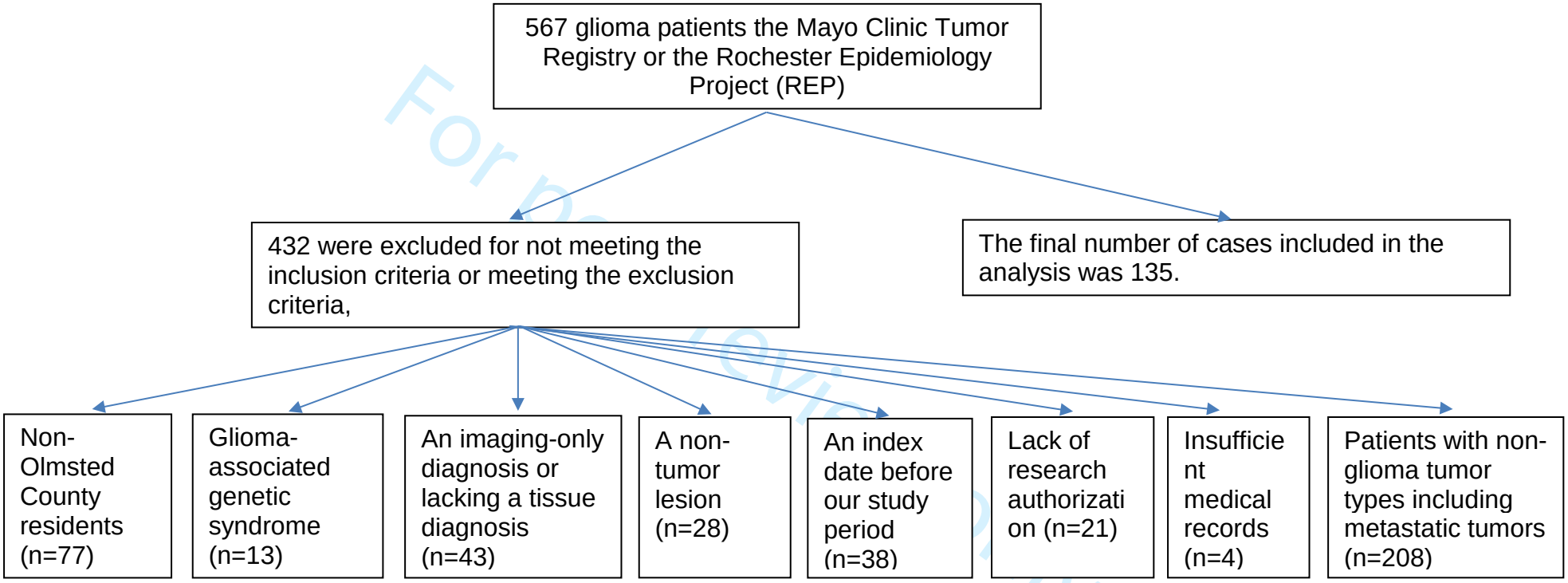
					but not by weighted median estimate (OR 0.96, 95% CI 0.91–1.01, P = 0.114) or mode-based estimate (OR 0.97, 95% CI 0.92–1.02, P = 0.194)	the risk of developing glioma
c. Interaction / effect modification						
Schoemaker, Europe, 2010 (4)	5 case-control studies (4 countries in Europe)	Case: 1029 Control: 1668	ICD codes	1. MD diagnosed atopic conditions 2. 5 SNPs of glioma risk; rs4977756, 498872, 6010620, 4295627, 2736100,	1. For risk of glioma and any allergy, OR 0.66 (0.55-0.78) 2. For number of risk alleles and allergy, P<0.05 for 3 SNPs (rs4977756,498872,6010620)	Evidence for possible gene-environment interactions in glioma development
Lachance, USA, 2011(5)	3 case-control studies in USA	Case:855 (high-grade glioma) Control:1160	Pathologically confirmed glioma cases	1. MD diagnosed allergies 2. 10 SNPs of glioma risk; rs4809324, 4977756, 4295627, etc.	1. rs4977756, OR 0.40 (0.28-0.58) without the allele of risk (SNP) vs. 0.76 (0.59-0.97) with the allele of risk SNP 2. rs4809324, OR 0.44(0.29-0.68) with the SNP vs. 0.68(0.54-0.86) without the SNP	The inherited glioma risk variants in chromosome regions 9p21.3 (rs4977756) and 20q13.3 (rs4809324) may modify the inverse association of allergy and glioma
Dobbins, UK , 2010 (10)	US and UK based gene wide association studies. Case-control study	Cases: 1,878 Controls: 3,670	Histologically confirmed or based on unequivocal diagnostic imaging	SNPs that have been validated in previous studies associated with atopy, allergy, asthma, eczema and hay fever	No significant association with glioma risk was seen between rs7130588 and rs1588265 in either case–control series. An increased risk of glioma was observed between the atopic risk allele of rs1420101 and glioma risk A significant association between rs7216389 and glioma risk was shown in the combined dataset whereby an increased glioma risk was associated with the risk allele for asthma	This positive association between asthma and glioma is inconsistent. The inference from such a complex phenotype is not necessarily straightforward, and such observations could be a consequence of reverse causality.

eTable 2. Reasons for testing MRI among MRI negative controls (n=135)

Pain (headache)	Stroke (ischemia)	Cranial nerve, vision/ hearing issue	Dementia (memory), psychiatric	Dizziness , syncope	Spell, seizure	Others*	Research
31 (23%)	23 (17%)	22 (16.5%)	13 (9.5%)	13 (9.5%)	13 (9.5%)	10 (7.5%)	10 (7.5%)

* Others include developmental concern pituitary concern, and deep brain stimulation.

eTable3. Number of Cases and Controls after applying the exclusion criteria



STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) Checklist

A checklist of items that should be included in reports of observational studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Section and Item	Item No.	Recommendation	Reported on Page No.
Title and Abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4
Introduction			
Background/Rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study Design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	-
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	8-10
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	-
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	-
		Case-control study—For matched studies, give matching criteria and the number of controls per case	8-9
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-11

Section and Item	Item No.	Recommendation	Reported on Page No.
Data Sources/ Measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-10
Bias	9	Describe any efforts to address potential sources of bias	9-10
Study Size	10	Explain how the study size was arrived at	8
Quantitative Variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	12
Statistical Methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	12
		(*b*) Describe any methods used to examine subgroups and interactions	12
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	9-10
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12-13
		(b) Give reasons for non-participation at each stage	29
		(c) Consider use of a flow diagram	29
Descriptive Data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12-13, 23
		(b) Indicate number of participants with missing data for each variable of interest	23
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	-
Outcome Data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	-
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	12-13
		Cross-sectional study—Report numbers of outcome events or summary measures	-

Section and Item	Item No.	Recommendation	Reported on Page No.
Main Results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13-14
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other Analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13
Discussion			
Key Results	18	Summarise key results with reference to study objectives	14-16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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Asthma and Risk of Glioma: A Population-Based Case-Control Study

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Asthma and Risk of Glioma: A Population-Based Case-Control Study

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Contributorship statement: All authors meet the criteria for authorship based on the following four requirements: (1) substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; (2) drafting the work or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Specifically, Y.J.J. had full access to all of the data in the study, takes responsibility for the integrity of the data and the accuracy of the data analysis, and had authority over manuscript preparation and the decision to submit the manuscript for publication.

Study concept and design: C.W., D.L., and Y.J.J.

Acquisition, analysis, or interpretation of data: H.K., C.R., Y.S., H.S., C.W., S.S., K.K., E.R., D.L., and Y.J.J. Drafting of the manuscript: H.K., C.R., H.S., C.W., E.R., D.L., and Y.J.J.

Critical revision of the manuscript for important intellectual content: all authors.

Statistical analysis: C.W., K.K., and E.R.

Study supervision: C.W., D.L., and Y.J.J.

Competing interest statement: None Declared.

Abstract (257/300 words)

Objectives: Literature suggests an inconsistent, but largely inverse, association between asthma and risk of glioma, which is primarily due to methodological inconsistency in sampling frame and ascertainment of asthma.

Objective of the study was to clarify the association between asthma and risk of glioma by minimizing methodological biases (eg, recall and detection bias).

Design: A population-based case-control study

Setting: General population in Olmsted County, Minnesota, US

Participants: All eligible biopsy-proven incident glioma cases (1995-2014) and two sets of controls among residents matched to age and sex (1st set: community controls without glioma; 2nd set: MRI-negative controls from the same community).

Methods: The predetermined asthma criteria via medical record review were applied to ascertain asthma status of cases and controls. History of asthma prior to index date was compared between glioma cases and their matched controls using conditional logistic regression models. Propensity score for asthma status was adjusted for multivariate analysis.

Results: We enrolled 135 glioma cases (median age at index date: 53 years) and 270 controls. Of the cases, 21 had a history of asthma (16%), compared to 36 of MRI controls (27%) [OR (95%CI): 0.48 (0.26-0.91), p=0.03]. With MRI controls, inverse association between asthma and risk of glioma persisted after adjusting for the propensity score for asthma status, but did not reach statistical significance probably due to the lack of statistical power (OR [95%CI]: 0.48 [0.21-1.09]; p=0.08) Based on

comparison of characteristics of controls and cases, community controls seem to be more susceptible to a detection bias.

Conclusions: While differential detection might account for the association between asthma and risk of glioma, asthma may potentially pose a protective effect on risk of glioma. Our study results need to be replicated by a larger study.

Key Words (3-5 words): glioma, asthma, epidemiology, sampling, allergy

Strengths and limitations of this study:

1. This is a population-based case-control study performed in a self-contained community to address selection bias.
2. Predetermined asthma criteria (exposure) and biopsy-proven glioma case ascertainment (outcome) were used along with two different sets of controls to assess the impact of detection bias.
3. Laboratory data and lung function testing results not included in the study results.
4. Despite a population-based study, our study includes a small number of glioma cases which did not allow us to fully address asthma heterogeneity.

Data sharing statement: No additional data available.

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INTRODUCTION

Glioma is the most common primary intracranial malignant tumor (1). Approximately, 17,600 new cases of gliomas are diagnosed per year with a 5-year survival rate of 27% (2). Although treatment options have improved with better understanding of the molecular biology of these tumors, malignant glioma remains incurable with largely unknown etiology (3).

Many previous case-control studies that assessed the association between *asthma* and development of glioma suggested inverse associations. However, some methodological limitations of previous studies might account for some of the inconsistent results and obscure previously reported inverse associations between asthma and the risk of glioma. In addressing the methodological limitations of previous studies, we had a few specific concerns: 1) *self-reported asthma ascertainment* as exposure instead of predetermined criteria for asthma based on medical record review (eg, recall bias), and 2) *detection bias* stemming from differential detection of exposure as a result of differential health care access between glioma cases and controls. For example, almost a quarter of caregivers whose children were admitted to hospital with a diagnosis of asthma reported that their children did not have asthma.(4) Similarly, 7.5% of high-schoolers who had recurrent asthma symptoms were not diagnosed with asthma, (5) and this is true for adults as well.(6) In previous studies assessing association between asthma and glioma, almost all studies were based on self-reported asthma status, which can be also influenced by the rapidly debilitating nature of glioma causing cognitive and memory impairment potentially leading to misclassification of

asthma. eTable 1 summarizes literature regarding asthma and risk of glioma as well as their study designs. In terms of detection bias, individuals with asthma might be more likely to seek medical care and evaluation for their current or previous respiratory symptoms raising neurological symptoms related to glioma as outcome and undergoing an imaging study.

To address these methodological limitations in assessing the relationship between asthma and risk of glioma, we designed this study as a population-based case-control study that enrolled all eligible biopsy-proven incident glioma cases (both adult and pediatric cases) and two sets of matched-controls from the community population, i.e., (1) community controls who do not have history of glioma, and (2) MRI-controls with negative test results. We postulate that MRI-controls are more suitable (than community controls) as they are likely to be more similar to cases with regard to the likelihood of detection of outcome event due to similar health care access to glioma cases (ie, minimizing detection bias) as suggested in the literature.(7-9) This study design allows examining a potential detection bias. In addition, we utilized predetermined asthma criteria (delineated in Table 1) and performed a comprehensive medical record review to objectively ascertain the asthma status. Our study specifically focused on the association between asthma, not overall allergies, and the risk of glioma and despite the small sample size, we explored to assess the relationship between heterogeneity of asthma and the risk of glioma.

METHODS:

Study Setting

Olmsted County, southeastern Minnesota is an excellent setting to conduct a population-based epidemiologic study because medical care is virtually self-contained within the community. When patients register with any health care providers in the community, they or their parents/legal guardian are asked to grant authorization of use of their medical records for research. Authorization is granted by over 95% of all individuals. Comprehensive medical records research at Olmsted County is made possible through the Rochester Epidemiology Project (REP), which has been continuously funded by NIH and maintained since 1966.(10) The REP database consists of all medical records from two major medical centers (Mayo Clinic Rochester and Olmsted Medical Center) and their affiliated hospitals. Only those individuals with current research authorization were included in this study. The population demographics of Olmsted County and of those included the REP database have been previously described.(10)

Study Design and Study Subjects:

A retrospective population-based case-control design was employed. Patients diagnosed with glioma (cases) during1995-2014 and their two matched controls (see Case Ascertainment and Selection of Controls) were identified from the REP database representing Olmsted County, MN residents. Asthma status prior to index date of cases and their matched controls was ascertained by predetermined asthma criteria and its frequency was compared between cases and controls (each control group and both control groups separately). The Olmsted Medical Center and Mayo Clinic Institutional Review Boards approved this study.

Patient and public involvement

No patients or the public were involved in the study protocol design, the specific aims or the research questions, and the plans for the design or implementation of the current study. No patients or the public were involved in the interpretation of the results of the study or preparation of the manuscript. There are no plans to disseminate the results of the research to study participants.

Case Ascertainment

All Olmsted County residents who developed glioma during the study period of January 1st, 1995, to December 31st, 2014, were identified from the Mayo Clinic Tumor Registry and the REP using medical index search codes. The medical index search codes used for this study include HICDA (Mayo's modified version of the Hospital Adaptation of the Internal Classification of Diseases, used at Mayo since 1975) and ICD-9 codes. Each preliminary case was reviewed to ascertain cases that met the enrollment criteria, including 1) Olmsted County residency at the index date and one year prior to index date, with 2) research authorization, and 3) pathology confirmed glioma cases [e.g., astrocytoma, oligodendroglioma, gliomatosis cerebri, mixed gliomas (oligoastrocytoma), and glioblastoma] of brain and spinal cord. The index date was defined as the date of glioma diagnosis by pathology reporting. World Health Organization (WHO) classification of primary brain tumors according to histology and grade was applied (i.e., Grade I, II-III, Grade IV).(11)

The exclusion criteria included: 1) non-Olmsted County residents at or one year prior to index date, 2) individuals without research authorization, 3) insufficient medical records for determining case and exposure status, 4) non-glioma tumor types (e.g., recurrent glioma, metastatic brain tumor, ependymoma, and non-glial brain tumor [e.g., meningioma]), 5) glioma-related hereditary syndrome (e.g., tuberous sclerosis, neurofibromatosis types 1 and 2), 6) absence of a tissue diagnosis, and 7) clinical conditions making asthma ascertainment difficult (see Table 1).

Selection of Controls

Two controls per case, matched based upon birth year, sex, and registration year, to ensure similar exposure to health care between cases and controls, were identified in the REP database to assess the potential detection bias which might have attenuated or obscured the previously reported inverse association between asthma and risk of glioma, especially an inverse association. The first cohort of controls included subjects selected from the population in Olmsted County who did not have any history of glioma by HICDA and ICD-9 codes for initial screening confirmed by medical record review ("community control"). The second controls were subjects who had undergone brain or neck imaging, identified by CPT codes completed within one year of their corresponding case diagnosis, who had normal findings ("MRI control"). The index date for control was same as the one of their corresponding case. Controls were held to the same enrollment and exclusion criteria as cases. Reasons for MRI imaging among the MRI controls were reviewed and reported (eTable 2).

Asthma Ascertainment

We determined asthma status prior to the index date for both cases and controls according to predetermined asthma criteria (PAC) outlined in Table 1. Both definite and probable asthma statuses were considered as asthma as most probable asthma became definite asthma over time(12). This asthma criteria was originally developed by Drs. John Yunginger and Charles Reed(12) and has shown excellent construct validity and reliability (0.72-0.92) of the criteria (12-15). The onset date of asthma (asthma inception date) by PAC, was defined as the earliest constellation of symptoms found in the medical record that met the PAC, which provides a clearer temporal relationship between onset of asthma and the risk of glioma.

Active (or current) asthma was defined as the presence of any asthma-related events, including asthma symptoms (e.g., wheezing, night cough, dyspnea), use of asthma medications (e.g. short-acting beta agonists, inhaled corticosteroids, leukotriene inhibitors), and/or outpatient, inpatient or emergency department (ED) visits for asthma within 12 months of the index date. Poorly controlled asthma was defined as the presence of any asthma symptoms, use of systemic corticosteroid for asthma symptoms, or unscheduled visits for asthma, including ED or hospitalization for asthma, within six months prior to index date (16).

For those patients with an electronic medical record (EMR) at Mayo Clinic available since 1997, we used a natural language processing (NLP) algorithm to determine PAC (NLP-PAC; automatic chart review for EMR by computer).This was developed and validated for automatic chart review for determining PAC by computer and the details have been recently reported (17). Briefly, validation performance of NLP-PAC was promising with 97%, 95%, 90%, and 98% for sensitivity, specificity, positive

predictive value, and negative predictive value of NLP algorithm against manual chart review. This NLP-PAC algorithm has been externally validated by assessing validity in a different study setting (Sioux Falls, South Dakota) (18)

Other variables

Demographics including sex, age, race and clinical characteristics including family history of asthma, and a physician diagnosis of other atopic conditions (eczema and allergic rhinitis) were reported. A family history of asthma, smoking status within 3 months prior to index date (second-hand smoking included for pediatric population), pneumococcal and seasonal influenza vaccine status as a surrogate marker for access to health care service, co-morbid conditions (history of epilepsy, stroke or transient ischemic attack (TIA), rheumatoid arthritis, lupus erythematosus, multiple sclerosis, and diabetes) were collected by abstractors. Factors related to socioeconomic status (SES) were measured using an individual-level housing-based socioeconomic status measure we developed and validated, called HOUSES. (19, 20) This data was formulated as standardized z-scores based on the address information at index date using real property data (i.e. value, size, number of bedrooms and bathrooms) after geocoding.(19) Higher HOUSES values equate to higher socioeconomic status.

Statistical Analysis

We summarized the characteristics of cases and two sets of controls using descriptive statistics. We performed conditional logistic regression to assess the association of asthma status and its other characteristics with risk of glioma. Odds ratios (OR) and

their corresponding 95% confidence intervals (95% CIs) were presented. To minimize the impact of confounders for the association between asthma and risk of glioma, the propensity scores for asthma status were first calculated and then adjusted in the analysis. A gradient boosting machine (GBM) approach allowing interaction was used for calculating the propensity scores using sociodemographic variables (listed in Table 2; race, education, HOUSES, seasonal flu vaccination, PPSV23 vaccination, and smoking exposure).(21) We also looked at differences between subgroups (i.e., stratified by tumor grade) although no formal comparisons were made because of the small sample sizes. All analyses were performed using SAS statistical software package (Ver 9.4; SAS Institute, Inc., Cary, NC) and R package (R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study subjects

A total of 567 patients were found in the Mayo Clinic Tumor Registry or the Rochester Epidemiology Project (REP) with a diagnosis code for glioma. Of these, 432 were excluded for not meeting the inclusion criteria or meeting the exclusion criteria, with 135 as our final cases including 19 (14%) pediatric cases (<18 years) (eFigure1).

The sociodemographic characteristics are summarized in Table 2. When we compared each control set (i.e., community controls and MRI controls) with cases in terms of socioeconomic status (HOUSES) and access to health care (seasonal flu vaccine and PPSV23), we found MRI controls were more similar to cases than population controls.

This suggests that MRI controls may be more representative of the source population to compare against the glioma cases in this study.

Comparison of prevalence of asthma between glioma cases and controls

Twenty one (16%) of the 135 cases had asthma, whereas 36 (27%) of the 135 MRI controls and 17 (13%) of the 135 community controls had asthma (OR [95%CI]: 0.48 [0.26-0.91]; p=0.03 for MRI controls and OR [95%CI]: 1.28 [0.64-2.59]; p=0.48 for community controls; see Table 3). We assessed the association of asthma status with cases (vs. MRI controls) after adjusting for the propensity score for asthma status, and found asthma remained to be protective of glioma, but did not reach statistical significance probably due to the lack of statistical power (OR [95%CI]: 0.48 [0.21-1.09]; p=0.08) (Table 4).

When we stratified cases by WHO grade (I [n=19], II-III [n=40], and IV [n=76]), glioma cases were less likely to have a history of asthma compared to MRI controls in all grades (16% [cases] vs. 47% (0.21, 0.05-0.96) [MRI controls], 18% vs. 30% (0.50, 0.17-1.43), 15% vs. 20% (0.69, 0.29-1.62) for Grade I, II-III, and IV, respectively). Active asthma (OR [95% CI]: 0.40 [0.17-0.93]) was associated with a stronger inverse association with glioma risk compared to inactive asthma (0.58 [0.26-1.28]) when using non-asthmatic group as the reference group. Poorly controlled asthma (0.1 [0.02-1.1]) showed similar effect, but did not reach statistical significance. As an association between asthma and glioma has been reported to change directions near the detection of glioma (22), we assessed the association of asthma and risk of glioma after excluding those with <2 years of latency in our study, but no difference was found. In

pediatric subjects, there was no difference in the proportions of asthma between cases and both control groups (ie, 14% in all subgroups [cases, MRI controls, and community controls]).

Comparison of prevalence of other comorbidities and smoking status between glioma cases and controls

While allergic rhinitis, eczema, and family history of asthma for cases with comparison with MRI controls showed toward more inverse association with glioma, they all failed to reach statistical significance in part due to small sample size (Table 3). Stroke or TIA was significantly associated with risk of glioma in comparison with either control group, but diabetes was not. Other comorbidities assessed such as epilepsy, rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis were very rare in our cohort and were not analyzed. Glioma cases were less likely to have a history of smoking exposure, especially compared to MRI controls (OR [95% CI]: 0.5 [0.3-0.9]).

DISCUSSION

In this study, using two different control sets, while asthma tends to be inversely associated with the risk of glioma based on MRI controls, such association was not supported in community controls. As MRI controls were more similar to cases (than community controls), our study results may uphold previous study results supporting an inverse association between asthma and risk of glioma. At the same time, these differential results depending on controls account for inconsistent results and their source (selection bias).

Patients with asthma may seek health care more often than those without asthma, resulting in an increased chance of detecting glioma (and other health outcomes) (detection bias)(23). If detection bias occurred in studying an association between asthma and the risk of glioma, one would expect an increased detection of asthma among MRI controls (e.g., a marker for care seeking) leading to a null association (ie, obscuring an inverse association) and a lower detection of asthma among community controls resulting in a positive association between asthma and risk of glioma. However, our study results were contrary to this anticipation (i.e., an inverse association between asthma and the risk of glioma using MRI controls and no association in community controls), and thus, MRI controls might negate potential detection bias. In addition, while our previous study from the same study setting showed non-differential access to health care between asthmatics and non-asthmatics(24), as MRI controls are more similar to glioma cases in terms of clinical and socioeconomic variables, we believe MRI controls may be more suitable and representative for a source population from who glioma cases were drawn (eg, similar education, HOUSES, and rate of seasonal flu vaccine). One may be concerned about indications for MRI among MRI controls in interpretation of the study results. We assessed (eTable 2) whether indications for MRI among MRI controls are associated with asthma, leading to higher prevalence of asthma among MRI controls than among cases, resulting in an inverse association. However, prevalence of common indications for MRI such as headache (migraine), stroke, dementia, and seizure in MRI controls were overall higher than or similar to cases, except migraine. This suggests MRI controls might be less biased controls (than

community controls) which are likely to minimize a detection bias obscuring an inverse association between asthma and the risk of glioma.

To minimize misclassification bias for asthma status from self-report or ICD codes, we utilized an objective method for asthma ascertainment by applying predetermined asthma criteria (PAC) through comprehensive medical record review. Apart from the association between asthma status and risk of glioma, in the analysis using MRI controls, active asthma showed a more protective effect than inactive asthma and similarly poorly controlled asthma posed a more protective effect than not-poorly controlled asthma, although it did not reach statistically significance. Therefore, overall, our results on an inverse association between asthma and the risk of glioma based on MRI controls might uphold prior observations supporting such inverse associations.

The relationship between asthma and risk of malignancy in general varies depending on the type of malignancy. For example, asthma has been shown to increase the risk for lung cancer while inverse association of asthma with multiple tumors has been reported including pancreatic or stomach cancer, acute lymphoblastic leukemia, gliomas, non-Hodgkin's lymphoma, and even colorectal cancer(25, 26). Hyperactive immune systems in patients with allergic disorders could cause a lower incidence of cancers(27). In fact, presence of any allergic disorder (eczema, allergic rhinitis or asthma) in studies with twins or similar genetic and environmental factors have demonstrated lower association with gliomas(28). However, in our study, atopic conditions other than asthma were not associated with the risk of glioma presumably due to small sample size and

methodological limitations (eg, undetected allergic rhinitis which might be identified by self-report). Along these lines, a family history of asthma as a marker for shared genetics or environment (29) was not associated with the risk of glioma in our study which is consistent with the literature (30, 31).

Temporality between asthma (by self-report) and glioma previous studies reported could be inconsistent in terms of the total duration of asthma and age at asthma onset. (32-34) For example, Wigertz et al reported inverse association for both current and past asthma related with glioma while the reduced risk of glioma related to other allergic conditions such as eczema, hay fever, and overall allergy were confined to current rather than past conditions. Our study results suggest that active (current) asthma, especially poorly controlled asthma posed the strongest protective effect, compared to non-asthmatics and inactive (past) asthma by our predetermined criteria. As these findings are based on predetermined criteria for asthma status and asthma control status (not relying on self-report and unclear temporality), the results have greater reproducibility and provide a better insight into the relationship between asthma status, control status, and the risk of glioma. While no association between pediatric glioma cases and asthma was found, this needs to be replicated given small sample size of pediatric cases.

The mechanisms underlying the potential inverse association is unknown. It is important to determine which one (asthma vs. its associated risk factors [i.e., confounders]) is responsible for this observed potential inverse association. As our

study is epidemiological and focused on clarification of inconsistent results of the literature, this study question needs to be addressed in the future. Prior studies suggest that antihistamines have been implicated to worsen glioma burden in patients with allergies with inconsistent result (35-38) while biological plausibility is yet to be identified. Also, literature suggests that immunoglobulin E (IgE) plays a role in reducing the risk of cancers and use of IgE monoclonal antibodies for the passive immunotherapy in murine models has been found to kill tumor cells in multiple previous studies via antibody dependent cellular toxicity.(39),(40) Along these lines, cytokines associated with Th2-immune responses have shown anti-tumor activity(41). For example, IL-5 which is a cytokine produced by lymphoid cells has been found to recruit eosinophils and create a microenvironment that prevents tumor formation in the lung. However, whether this type of anti-tumor activity is applicable to glioma needs to be studied. Though the underlying mechanisms remain poorly understood, our work clarified the inconsistency of the literature on the association between asthma and risk of glioma and provides an insight into a potential inverse association between asthma and risk of glioma.

Our study has some inherent limitations as a retrospective study. We did not include laboratory or lung function data to measure Th2 immune responses or other inflammatory responses, which might help us to discern the study results. The power of our study was limited due to a small number of glioma cases even if our study included all eligible population-based cases. These study results need to be replicated with a larger number of glioma cases in future studies. As our study setting mostly consists of

Caucasian patients, generalizability of our study results to other settings or ethnic groups needs to be cautious. Our study also has important strengths. The study setting has unique advantages, including a self-contained health care environment and a medical record linkage system. This is also a population-based study design, which minimizes a selection bias. In addition, as we only included incident cases of glioma and determined index date of asthma as well, we were able to assess temporality on the relationship between asthma and risk of glioma. We used two sets of controls to mitigate or assess detection bias as described above. In addition, ascertainment of asthma status by using the PAC was performed independent of asthma status by a physician diagnosis of asthma, which minimized an observational bias.

Conclusion

Our study results suggest that asthma may pose a protective effect on the risk of developing glioma but the results need to be replicated in a larger study. In addition, our study results clarify the rationale for the inconsistent results on the relationship between asthma and risk of glioma.

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Table 1. Predetermined Asthma Criteria

Patients were considered to have *definite* asthma if a physician had made a diagnosis of asthma and/or if each of the following three conditions were present, and they were considered to have *probable* asthma if only the first two conditions were present:

1. History of cough with wheezing, and/or dyspnea, OR history of cough and/or dyspnea plus wheezing on examination,
2. Substantial variability in symptoms from time to time or periods of weeks or more when symptoms were absent, and
3. Two or more of the following:
   - Sleep disturbance by nocturnal cough and wheeze
   - Nonsmoker (14 years or older)
   - Nasal polyps
   - Blood eosinophilia higher than 300/uL
   - Positive wheal and flare skin tests OR elevated serum IgE
   - History of hay fever or infantile eczema OR cough, dyspnea, and wheezing regularly on exposure to an antigen
   - Pulmonary function tests showing one FEV_1 or FVC less than 70% predicted and another with at least 20% improvement to an FEV_1 of higher than70% predicted OR methacholine challenge test showing 20% or greater decrease in FEV_1
   - Favorable clinical response to bronchodilator

Patients were excluded from the study if any of these conditions were present:

- Pulmonary function tests that showed FEV_1 to be consistently below 50% predicted or diminished diffusion capacity
- Tracheobronchial foreign body at or about the incidence date
- Hypogammaglobulinemia (IgG less than 2.0 mg/mL) or other immunodeficiency disorder
- Wheezing occurring only in response to anesthesia or medications

The following diseases excluded the patient from study if they occurred before the incidence date:

- Bullous emphysema or pulmonary fibrosis on chest radiograph
- PiZZ $alpha_1$-antitrypsin
- Cystic fibrosis
- Other major chest disease such as juvenile kyphoscoliosis or bronchiectasis

FVC forced vital capacity; FEV1, forced expiratory volume in 1 sec.

Table 2. Sociodemographic characteristics of study subjects and their associated odds ratios of glioma by different set of controls (conditional logistic regression matching age and sex)

	Cases (n=135)	MRI controls (n=135)	OR (95%CI) for MRI controls	P value	Community controls (n=135)	OR (95%CI) for community controls	P value
Age, years, median (IQR)	53 (32, 68)	53 (32, 68)	-	-	53 (32, 68)	-	-
Female, n (%)	61 (45)	61 (45)	-	-	61 (45)	-	-
White, n (%)	126 (93)	123 (91)	1.4 (0.6-3.4)	0.49	119 (88)	2.2 (0.8-5.7)	0.11
Education							
Missing	20	3	-	-	10	-	-
High School or less	31 (27)	31 (23)	1.5 (0.6-3.3)	0.31	47 (38)	0.3 (0.1-0.7)	0.003
Some college	36 (31)	37 (28)	1.0 (0.5-1.8)	0.77	33 (26)	0.5 (0.2-1.1)	0.05
College completion	13 (11)	24 (18)	0.6 (0.2-1.3)	0.18	23 (18)	0.3 (0.1-0.8)	0.007
Graduate education	35 (30)	40 (30)	(ref)		22 (18)	(ref)	
HOUSES, Z (median, IQR)	-0.2 (-1.7, 2.3)	-0.8 (-2.6,2.3)		0.17	-0.6 (-2.7,1.8)		0.05
HOUSES, n (%)							
Missing	5	6	-	-	6	-	-
Q1 (lowest SES)	26 (20)	38 (30)	0.5 (0.3-1.2)	0.11	33 (26)	0.6 (0.3-1.3)	0.19
Q2	33 (25)	30 (23)	0.9 (0.5-1.8)	0.81	34 (26)	0.8 (0.4-1.7)	0.52
Q3	35 (27)	26 (20)	1.1 (0.6-2.1)	0.75	36 (28	0.8 (0.4-1.5)	0.44
Q4	36 (28)	35 (27)	(ref)	(ref)	26 (20)	(ref)	
Seasonal flu vaccine, n (%)	63 (47)	62 (46)	1.0 (0.6-1.7)	0.89	50 (37)	1.7 (1.0-3.1)	0.06
PPSV23[a], n (%)	33 (24)	39 (29)	0.7 (0.3-1.4)	0.29	30 (22)	1.2 (0.6-2.5)	0.59
Smoking exposure, n (%)							
Undocumented	4 (3)	3 (2)	-	-	12 (9)	-	-
Yes	48 (36)	67 (50)	0.5(0.3-0.9)	0.01	52 (39)	0.8 (0.4-1.3)	0.33
No	83 (62)	65 (48)	(ref)	(ref)	71 (53)	(ref)	

[a] Pneumococcal polysaccharide vaccine 23; Percentages may not add up to 100 due to rounding; Odds ratios and p-values for testing association of each variable with risk of glioma were estimated using conditional logistic regression models to take into account matching between cases and controls. Since age and gender were matching factors, their ORs and p-values are not presented.

Table 3. Association of asthma with glioma cases compared to different set of controls (conditional logistic regression matching age and sex)

	Cases (n=135)	MRI controls (n=135)	OR (95%CI) for MRI controls	P value	Community controls (n=135)	OR (95%CI) for Community controls	P value
Asthma PAC[a], n (%)	21 (16)	36 (27)	0.5 (0.3-0.9)	0.02	17 (13)	1.3 (0.6-2.6)	0.48
Asthma activity, n (%)							
No asthma	114 (84)	99 (73)	(ref)	(ref)	118 (87)	(ref)	(ref)
Inactive asthma	11 (8)	16 (12)	0.6 (0.3-1.3)	0.17	8 (6)	1.4 (0.5-3.8)	0.46
Active asthma	10 (7)	20 (15)	0.4 (0.2-0.9)	0.03	9 (7)	1.1 (0.4-3.2)	0.79
Asthma control, n (%)							
No asthma	114 (84)	99 (73)	(ref)	(ref)	118 (87)	(ref)	(ref)
Not poorly controlled asthma	19 (14)	29 (21)	0.6 (0.3-1.1)	0.11	14 (10)	1.5 (0.7-3.0)	0.31
Poorly controlled asthma	1 (1)	7 (5)	0.1 (0.02-1.1)	0.05	3 (2)	0.3 (0.04-3.5)	0.38
Eczema, n (%)	11 (8)	17 (13)	0.6 (0.3-1.4)	0.22	7 (5)	1.7 (0.6-4.6)	0.32
Allergic rhinitis, n (%)	28 (21)	30 (22)	1.0 (0.5-1.6)	0.76	23 (17)	1.3 (0.7-2.4)	0.43
Family history of asthma, n (%)							
Undocumented	34 (25)	36 (27)	-	-	51 (38)	-	-
Yes	12 (9)	15 (11)	0.8 (0.3-1.7)	0.49	7 (5)	1.5 (0.5-4.1)	0.46
No	89 (66)	84 (62)	(ref)	(ref)	77 (57)	(ref)	(ref)

Table 4. Multivariable analysis for comparing asthma and risk of glioma using MRI controls

	Adj. Odds Ratio	95% CI	P-value
Asthma PAC (ref="No")	0.48	0.21 -1.09	0.08
Propensity scores*	1.03	0.11- 9.54	0.98

*Propensity scores were formulated based on Race, education, HOUSES, seasonal flu vaccine, PPSV23, and smoking exposure status to control confounders and covariates and entered the model as a variable.

eTable 1. Summary of literature of epidemiologic studies on asthma and risk of glioma

Authors	Study design	Study subjects (data source)	Definition of glioma	Definition of asthma	Results (effect size)	Conclusion
A. Statistically significant inverse association						
Adults						
1.McCarthy et al, 3 countries (US, Sweden, Denmark), 2011(1)	Case-control study	-Cases: 410 (five case-control studies) -Controls: 840 (same hospital, random-digit-dialing, friends, or population-based) -Adults only	Histologically confirmed glioma (oligodendroglioma, anaplastic oligodendroglioma)	Survey: history of asthma (not clear)	aOR (95% CI): 0.4 (0.2, 0.7) (adjusted for age, group, gender, and site)	History of asthma was associated with a decreased risk of glioma
2.Wiemels et al, USA, 2002(2)	Population-based case-control study	-Cases: 405 (cancer registry) -Controls: 402 (random digit dialing methods) -Adults only	Glioma confirmed by the Northern California Cancer Center's rapid case ascertainment system	Survey: history of wheezing	aOR (95% CI): 0.57 (0.38-0.86) (adjusted for age, gender, and ethnicity)	Cases were less likely than controls to report wheezing (history of asthma not available)
3.Safaeian et al, USA, 2013(3)	Case-control study	-Cases: 851 with European ancestry (two case-controls studies and three prospective cohort studies) -Controls: 3,977 (same hospitals, driver identification records, or Health Care Financing Administration Medicare Records) -Adults only	Histologically confirmed glioma	Survey: history of asthma	aOR (95%CI): 0.58 (0.42-0.81) (adjusted for age, gender, and study)	Reporting asthma was associated with reduced risks of glioma.
4.Wigertz et al, 5 countries (Denmark, Norway, Finland, Sweden, and England), 2007(4)	Population-based case-control study (part of INTERPHONE study)	-Case:1,527 (treating clinics) -Control:3,309 (population registers) -Adults only	Glioma confirmed by cancer registries	Survey: history of asthma	1. aOR (95%CI): 0.65 (0.51-0.82) overall 2. aOR (95%CI): 0.68 (0.51-0.91) for current asthma 3. aOR (95%CI): 0.53 (0.34-0.80) for past asthma (adjusted for age, sex, education, country, and region within country)	There were reduced risks for glioma related to both current and past asthma.
5.Schoemaker et al, UK, 2006(5)	Population-based case-control study	-Cases: 965 (hospitals or cancer registry) -Controls: 1,716 (general practitioner patient lists) -Adults only	Glioma by ICD codes	Survey: history of asthma	aOR (95%CI): 0.71 (0.54-0.92) (adjusted for age, sex, category, region, Survey year, and Townsend deprivation category)	Risk of glioma was reduced in subjects reporting a history of asthma.

6.Turner et al, 5 countries (Australia, Canada, France, Israel, New Zealand), 2013(6)	International population-based case-control study (INTERPHONE)	-Cases: 793 (hospitals or nationwide (Israel)) -Controls: 2,374 (electoral lists, health/population registries, or random digit dialing) -Adults only	Histologically confirmed glioma or through unequivocal diagnostic imaging	Survey: history of asthma	aOR (95%CI): 0.72 (0.54-0.96) -By age of asthma onset a. <10yrs: 0.85 (0.55-1.33) b. 10-19yrs: 0.86 (0.45-1.64) c. 20+yrs: 0.58 (0.38-0.89) -By grade of glioma a. High grade: 0.62 (0.43-0.88) b. Low grade: 0.89 (0.58-1.37) (adjusted for education)	There was some evidence that the inverse associations with asthma strengthened with increasing age of asthma onset or grade of glioma and weakened with longer time since onset of asthma.
7.Brenner et al, USA, 2002(7)	Hospital-based case-control study	-Cases: 489 (3 hospitals) -Controls (hospitalized for a non-malignant conditions) -Adults only	Histologically confirmed glioma	Survey: history of asthma	aOR (95%CI): 0.63 (0.43-0.92) (adjusted for age, sex, and postal code)	There was a significant inverse association between glioma and history of asthma.
B. Statistically non-significant inverse or positive association						
B.1. Adults						
8.Ryan et al, Australia, 1992(8)	Population-based case-control study	-Cases: 110 (cancer registry) -Controls: 417 (electoral roll) -Adults only	Histologically confirmed glioma	Survey: history of asthma	aRR (95% CI): 0.40 (0.1-1.1) (adjusted for age and sex)	A history of atopy or allergic phenomena may be associated with a decreased risk of glioma.
9.Schwartzbaum et al, Sweden, 2005(9)	Population-based case-control study	-Cases: 111 (brain tumor treatment center and regional cancer registries) -Controls: 422 (population registry) -Adults only	Glioblastoma multiforme	Survey: history of asthma	OR (95%CI): 0.64 (0.33-1.25)	Self-report asthma was inversely related to glioma. Three out of four SNPs previously associated with asthma supported inverse association between asthma and glioma
10.Berg-Beckhoff et al, German, 2009(10)	Population-based case-control study (part of INTERPHONE study)	-Cases: 365 (neurosurgical clinics) -Controls: 732 (population registries) -Adults only	Histologically confirmed glioma	Survey: history of asthma	aOR (95%CI): 0.65 (0.36-1.19) (adjusted for socioeconomic status, urban vs. rural, smoking history, and age at diagnosis)	The adjusted odds ratios did not reveal any statistical significant associations between asthma and the occurrence of glioma with yet pointing towards an inverse association.
11. Pouchieu et al, France, 2018(11)	Multicenter population-based case-control study (CERENAT study)	-Cases: 273 (cancer registry) -Controls: 546 (local electoral rolls) -Adults only	Histopathological diagnosis OR imaging and clinical diagnosis	Survey: history of asthma	aOR (95% CI): 0.70 (0.37-1.32) (adjusted for educational level and mobile phone use)	History of asthma had an inverse association with glioma, but this association was not statistically significant.
12.Schlehofe	International	-Cases:1,178 (hospitals or	Histologically	Survey: history of	RR (95%CI): 0.75 (0.55-	There was a statistically

r et al, 6 countries (Australia, Canada, France, Germany, Sweden, and USA), 1999(12)	population-based case-control study	cancer registries) -Controls: 1,987 (population-based controls using different methods depending on each center) -Adults only	confirmed glioma	asthma	1.03)	significant inverse association between glioma and asthma.
13. Cahoon et al, USA, 2014(13)	Retrospective cohort study	-4.5 million of male veterans of the USA -4,383 incident, primary brain cancer cases (95% glioma) developed -Adults only (18-100 years)	ICD codes	Discharge diagnosis code of asthma (≥2 years between diagnosis of asthma and end of follow-up)	RR (95%CI): 0.8 (0.6-1.07)	This study lends some support to an inverse association between asthma of long duration and risk of brain cancer (not exclusively glioma)
14.Cicuttini et al, Australia, 1997 (14)	Population-based case-control study	-Cases: 416 (cancer registry) -Controls:422 (electoral roll) -Adults only	Histologically confirmed glioma	Survey: history of asthma	aOR (95%CI): 0.8 (0.5-1.2) (adjusted for age and sex)	There was no significant association between asthma and the risk of developing glioma.
15.Il'yasova, USA, 2009(15)	Clinic-based case-control study with three sets of controls	Cases: 388 (two hospitals) Controls: 80 siblings and 191 friends recommended by patient, and 177 clinic-based controls (actively from orthopedic clinics and using flyers placed in clinics) -Adults only	ICD codes	Web-based or telephone survey: history of asthma	OR (95%CI) -Clinic-based controls: 1.90 (0.89-4.07) -Sibling controls: 0.43 (0.19–1.00) -Friend controls: 0.84 (0.47-1.50)	Asthma showed an inverse association only in the comparison with sibling controls, but not with clinic-based or friend controls. Clinic based controls generally better approximate the prevalence data for population-based groups.
16.Dobbins et al, UK and US, 2011(16)	Multicenter case-control series	-Cases: 1,878 (UK GWA study through INTERPHONE study and one US cancer center) -Controls: 3670 (UK Birth Cohort and US CGEMS study)	Histologically confirmed or based on diagnostic imaging	SNPs known to be related to asthma (rs7216389, rs1588265, rs1420101)	OR (95%CI) trend for rs7216389 (ORMDL3 at 17q21): 1.10 (1.01-1.19)	The observation provides evidence of a positive association between asthma and glioma
B.2. Children						
17.Harding et al, UK, 2008(17)	Population-based case-control study	-Cases: 326 (UK Childhood Cancer Study) -Controls: 6,292 (health authorities or health boars) -Children only	ICD-O codes for glioma	Survey: mother's report for child's history of asthma	aOR (95%CI): 0.90 (0.66-1.23) (adjusted for Townsend deprivation category)	Asthma by parental report was not associated with glioma.
18.Shu et al,	Population-	-Cases: 352 (cancer	Histologically	Survey: parent's	aOR (95%CI)	There was no association

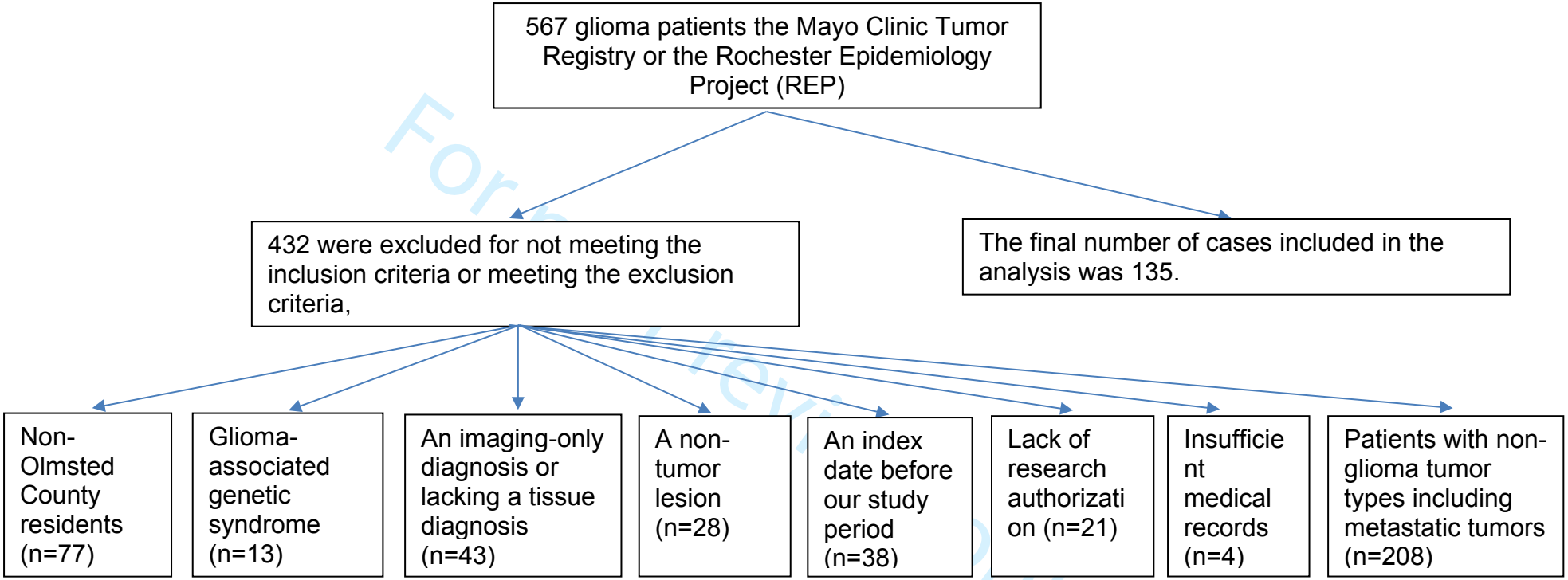
Denmark, Norway, Sweden, and Switzerland, 2014(18)	based case control study (CEFALO)	registries) -Controls: 646 (population registries) -Children only	confirmed glioma or through unequivocal diagnostic imaging	report for child's history of asthma	-Overall: 0.99 (0.54-1.82) -Current: 0.97 (0.42-2.25) -Past: 0.80 (0.36-2.22) (adjusted for living on a farm before age 6 and socioeconomic status)	between asthma and risk of glioma.
C. Systematic review and meta-analysis						
Author	**Study design**	**Study subjects**	**Conclusion**			
19.Zhang et al, 2017(19)	Meta-analysis of 9 case control and cohort studies	Cases: 8,435 Controls: 118,719	The pooled result indicated that asthma would reduce the risk of glioma by 33% (OR = 0.67, 95% CI = 0.59-0.75, *P* < 0.001)			
20.Chen et al, 2010(20)	Meta-analysis of 7 case–control studies	Cases: 5,317 Controls: 9,393	The pooled OR for glioma and asthma was 0.70 (95% CI: 0.62-0.79, *P*<0.001)			
21.Linos et al, 2007(21)	Meta-analysis of 5 case-control studies	Cases: 3,450 participants : 53,223	Pooled RR for glioma among those reporting a history of asthma compared with no such history was 0.68 (95% CI = 0.58-0.80, *P* <.001)			

eTable 2. Indications for testing MRI among MRI negative controls (n=135)

Pain (headache)	Stroke (ischemia)	Cranial nerve, vision/ hearing issue	Dementia (memory), psychiatric	Dizziness, syncope	Spell, seizure	Others*	Research
31 (23%)	23 (17%)	22 (16.5%)	13 (9.5%)	13 (9.5%)	13 (9.5%)	10 (7.5%)	10 (7.5%)

* Others include developmental concern pituitary concern, and deep brain stimulation.

eFigure1. Number of Cases and Controls after applying the exclusion criteria



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STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) Checklist

A checklist of items that should be included in reports of observational studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Section and Item	Item No.	Recommendation	Reported on Page No.
Title and Abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4
Introduction			
Background/Rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study Design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	-
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	8-10
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	-
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	-
		Case-control study—For matched studies, give matching criteria and the number of controls per case	8-9
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-11

Section and Item	Item No.	Recommendation	Reported on Page No.
Data Sources/ Measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-10
Bias	9	Describe any efforts to address potential sources of bias	9-10
Study Size	10	Explain how the study size was arrived at	8
Quantitative Variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	12
Statistical Methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	12
		(*b*) Describe any methods used to examine subgroups and interactions	12
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	9-10
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12-13
		(b) Give reasons for non-participation at each stage	29
		(c) Consider use of a flow diagram	29
Descriptive Data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12-13, 23
		(b) Indicate number of participants with missing data for each variable of interest	23
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	-
Outcome Data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	-
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	12-13
		Cross-sectional study—Report numbers of outcome events or summary measures	-

Section and Item	Item No.	Recommendation	Reported on Page No.
Main Results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13-14
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other Analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13
Discussion			
Key Results	18	Summarise key results with reference to study objectives	14-16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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