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Asthma and risk of glioma: a population-based case–control study

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ABSTRACT

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

Design A population-based case–control study.

Setting General population in Olmsted County, Minnesota, USA.

Participants All eligible biopsy-proven incident glioma cases (1995–2014) and two sets of controls among residents matched to age and sex (first set: community controls without glioma; second 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 with 36 of MRI controls (27%) (OR (95% CI) 0.48 (0.26 to 0.91), p=0.03). With MRI controls, an 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 to 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.

Strengths and limitations of this study

- ► This is a population-based case–control study performed in a self-contained community to address selection bias.
- ► 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.
- ► Laboratory data and lung function testing results not included in the study results.
- ► Despite a population-based study, our study includes a small number of glioma cases which did not allow us to fully address asthma heterogeneity.

INTRODUCTION

Glioma is the most common primary intracranial malignant tumour.[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 tumours, malignant glioma remains incurable with largely unknown aetiology.[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 healthcare 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. Online supplementary eTable 1 summarises 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 paediatric cases) and two sets of matched controls from the community population, that is, (1) community controls who do not have a 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 healthcare access to glioma cases (ie, minimising detection bias) as suggested in the literature.[7–9] This study design allows examining a potential detection bias. In addition, we used predetermined asthma criteria (PAC, delineated in box 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 epidemiological study because medical care is virtually self-contained within the community. When patients register with any healthcare providers in the community, they or their parents/legal guardian are asked to grant authorisation of use of their medical records for research. Authorisation 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 the National Institutes of Health and maintained since 1966.[10] The REP database consists of all medical records from two major medical centres (Mayo Clinic Rochester and Olmsted Medical Center) and their affiliated hospitals. Only those individuals with current research authorisation were included in this study. The population demographics of Olmsted County and of those included the REP database have been previously described.[10]

Box 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: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 dyspnoea, OR history of cough and/or dyspnoea 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.
   - Non-smoker (14 years or older).
   - Nasal polyps.
   - Blood eosinophilia higher than 300/µL.
   - Positive weal and flare skin tests OR elevated serum IgE.
   - History of hay fever or infantile eczema OR cough, dyspnoea 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 than 70% predicted OR methacholine challenge test showing 20% or greater decrease in FEV_1.
   - Favourable clinical response to bronchodilator.

Patients were excluded from the study if any of these conditions were present: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 anaesthesia or medications.

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

Study design and study subjects

A retrospective population-based case–control design was employed. Patients diagnosed with glioma (cases) during 1995–2014 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 PAC and its frequency was compared between cases and controls (each control group and both control groups separately).

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 1 January 1995 to 31 December 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 enrolment criteria, including (1) Olmsted County residency at the index date and 1 year prior to index date, with (2) research authorisation and (3) pathology-confirmed glioma cases (eg, 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. WHO classification of primary brain tumours according to histology and grade was applied (ie, Grade I, II–III, Grade IV).[11]

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

Selection of controls

Two controls per case, matched based on birth year, sex and registration year, to ensure similar exposure to healthcare 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 Current Procedural Terminology (CPT) codes completed within 1 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 enrolment and exclusion criteria as cases. Reasons for MRI imaging among the MRI controls were reviewed and reported (online supplementary eTable 2).

Asthma ascertainment

We determined asthma status prior to the index date for both cases and controls according to PAC outlined in box 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 (eg, wheezing, night cough, dyspnoea), use of asthma medications (eg, 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 hospitalisation for asthma, within 6 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 (secondhand smoking included for paediatric population), pneumococcal and seasonal influenza vaccine status as a surrogate marker for access to healthcare service, comorbid conditions (history of epilepsy, stroke or transient ischaemic 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] These data were formulated as standardised z-scores based on the address information at index date using real property data (ie, value, size, number of bedrooms and bathrooms) after geocoding.[19] Higher HOUSES values equate to higher SES.

Statistical analysis

We summarised 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. ORs and their corresponding 95% CIs were presented. To minimise 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 approach allowing interaction was used for calculating the propensity scores using sociodemographic variables (listed in table 1; race, education, HOUSES, seasonal influenza vaccination, PPSV23 vaccination and smoking exposure).[21] We also looked at differences between subgroups (ie, stratified by tumour grade) although no formal comparisons were made because of the small sample sizes. All analyses were performed using SAS statistical software package (V.9.4; SAS Institute, Cary, North Carolina, USA) 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 REP with a diagnosis code for glioma. Of these, 432 were excluded for not meeting the inclusion criteria or meeting the exclusion criteria, with

Table 1 Sociodemographic characteristics of study subjects and their associated ORs 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 to 3.4)	0.49	119 (88)	2.2 (0.8 to 5.7)	0.11
Education							
Missing	20	3	–	–	10	–	–
High school or less	31 (27)	31 (23)	1.5 (0.6 to 3.3)	0.31	47 (38)	0.3 (0.1 to 0.7)	0.003
Some college	36 (31)	37 (28)	1.0 (0.5 to 1.8)	0.77	33 (26)	0.5 (0.2 to 1.1)	0.05
College completion	13 (11)	24 (18)	0.6 (0.2 to 1.3)	0.18	23 (18)	0.3 (0.1 to 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 to 1.2)	0.11	33 (26)	0.6 (0.3 to 1.3)	0.19
Q2	33 (25)	30 (23)	0.9 (0.5 to 1.8)	0.81	34 (26)	0.8 (0.4 to 1.7)	0.52
Q3	35 (27)	26 (20)	1.1 (0.6 to 2.1)	0.75	36 (28	0.8 (0.4 to 1.5)	0.44
Q4	36 (28)	35 (27)	(ref)	(ref)	26 (20)	(ref)	
Seasonal influenza vaccine, n (%)	63 (47)	62 (46)	1.0 (0.6 to 1.7)	0.89	50 (37)	1.7 (1.0 to 3.1)	0.06
PPSV23*, n (%)	33 (24)	39 (29)	0.7 (0.3 to 1.4)	0.29	30 (22)	1.2 (0.6 to 2.5)	0.59
Smoking exposure, n (%)							
Undocumented	4 (3)	3 (2)	–	–	12 (9)	–	–
Yes	48 (36)	67 (50)	0.5 (0.3 to 0.9)	0.01	52 (39)	0.8 (0.4 to 1.3)	0.33
No	83 (62)	65 (48)	(ref)	(ref)	71 (53)	(ref)	

*Pneumococcal polysaccharide vaccine 23. Percentages may not add up to 100 due to rounding; ORs 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.
SES, socioeconomic status.

Table 2 Association of asthma with glioma cases compared with 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*, n (%)	21 (16)	36 (27)	0.5 (0.3 to 0.9)	0.02	17 (13)	1.3 (0.6 to 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 to 1.3)	0.17	8 (6)	1.4 (0.5 to 3.8)	0.46
Active asthma	10 (7)	20 (15)	0.4 (0.2 to 0.9)	0.03	9 (7)	1.1 (0.4 to 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 to 1.1)	0.11	14 (10)	1.5 (0.7 to 3.0)	0.31
Poorly controlled asthma	1 (1)	7 (5)	0.1 (0.02 to 1.1)	0.05	3 (2)	0.3 (0.04 to 3.5)	0.38
Eczema, n (%)	11 (8)	17 (13)	0.6 (0.3 to 1.4)	0.22	7 (5)	1.7 (0.6 to 4.6)	0.32
Allergic rhinitis, n (%)	28 (21)	30 (22)	1.0 (0.5 to 1.6)	0.76	23 (17)	1.3 (0.7 to 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 to 1.7)	0.49	7 (5)	1.5 (0.5 to 4.1)	0.46
No	89 (66)	84 (62)	(ref)	(ref)	77 (57)	(ref)	(ref)

*PAC, predetermined asthma criteria.

135 as our final cases including 19 (14%) paediatric cases (<18 years) (online supplementary eFigure 1).

The sociodemographic characteristics are summarised in table 1. When we compared each control set (ie, community controls and MRI controls) with cases in terms of socioeconomic status (HOUSES) and access to healthcare (seasonal influenza 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 to 0.91), p=0.03 for MRI controls and OR (95% CI) 1.28 (0.64 to 2.59), p=0.48 for community controls; see table 2). 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 to 1.09); p=0.08) (table 3).

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 with MRI controls in all grades (16% (cases) vs 47% (0.21, 0.05 to 0.96) (MRI controls), 18% vs 30% (0.50, 0.17 to 1.43), 15% vs 20% (0.69, 0.29 to 1.62) for grade I, II–III and IV, respectively). Active asthma (OR (95% CI) 0.40 (0.17 to 0.93)) was associated with a stronger inverse association with glioma risk compared with inactive asthma (0.58 (0.26 to 1.28)) when using non-asthmatic group as the reference group. Poorly controlled asthma (0.1 (0.02 to 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 paediatric 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)).

Table 3 Multivariable analysis for comparing asthma and risk of glioma using MRI controls

	Adjusted OR	95% CI	P value
Asthma PAC* (ref='No')	0.48	0.21 to 1.09	0.08
Propensity scores**	1.03	0.11 to 9.54	0.98

*PAC, Predetermined Asthma Criteria
**Propensity scores were formulated based on race, education, HOUSES, seasonal influenza vaccine, PPSV23 and smoking exposure status to control confounders and covariates and entered the model as a variable.

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 2). 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 analysed. Glioma cases were less likely to have a history of smoking exposure, especially compared with MRI controls (OR (95% CI) 0.5 (0.3 to 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 healthcare 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 (eg, 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 (ie, 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 healthcare 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 whom glioma cases were drawn (eg, similar education, HOUSES and rate of seasonal influenza vaccine). One may be concerned about indications for MRI among MRI controls in interpretation of the study results. We assessed (online supplementary 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 minimise a detection bias obscuring an inverse association between asthma and the risk of glioma.

To minimise misclassification bias for asthma status from self-report or ICD codes, we used an objective method for asthma ascertainment by applying 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 statistical 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 tumours has been reported including pancreatic or stomach cancer, acute lymphoblastic leukaemia, 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*[33] 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 with 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 paediatric glioma cases and asthma was found, this needs to be replicated given small sample size of paediatric cases.

The mechanisms underlying the potential inverse association is unknown. It is important to determine which one (asthma vs its associated risk factors (ie, 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 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 tumour cells in multiple previous studies via antibody-dependent cellular toxicity.[39 40] Along these lines, cytokines associated with Th2-immune responses have shown anti-tumour 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 tumour formation in the lung. However, whether this type of anti-tumour 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, generalisability 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 healthcare environment and a medical record linkage system. This is also a population-based study design, which minimises 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 minimised 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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Contributors 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, YJ 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-IW, DHL and YJ. Acquisition, analysis or interpretation of data: HK, CSR, YHS, HYS, C-IW, SS, KSK, ER, DHL and YJ. Drafting of the manuscript: HK, CSR, HYS, C-IW, ER, DHL and YJ. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: C-IW, KSK and ER. Study supervision: C-IW, DHL and YJ.

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