PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Asthma and Risk of Glioma: A Population-Based Case-Control Study
AUTHORS	Kaur, Harsheen; Lachance, Daniel; Ryan, Conor; Sheen, Youn Ho; Seol, Hee Yun; Wi, Chung-Il; Sohn, Sunghwan; King, Katherine; Ryu, Euijung; Juhn, Young

VERSION 1 - REVIEW

REVIEWER	Judith Schwartzbaum Ohio State University, USA
REVIEW RETURNED	17-Sep-2018

GENERAL COMMENTS	The objective of this research is not clearly defined. Presumably the authors are studying the association between asthma and glioma yet they refer to the literature on atopy and glioma in their introduction. Contrary to the authors' statements in paragraph 2, page 6, the evidence for an association between atopy and glioma is consistent and strong. This is the reason that Amirian et al. were able to publish a paper entitled, "Approaching a Scientific Consensus on the Association between Allergies and Glioma Risk…", which is cited by the authors who write, "an inverse association between history of allergy and risk of glioma was found in the majority of studies". Their supplemental eTable 1 misrepresents the "majority of studies" on atopy and glioma because it is not complete. Nonetheless, the topic of this manuscript is asthma and glioma, which differs from atopy and glioma. As the authors clearly know, there are several asthma subtypes which need to be separately evaluated to determine whether allergic asthma or asthma per se is associated with glioma. Because the authors do not distinguish among asthma subtypes, it is difficult to interpret their results. That is, are the differences between the two types of controls attributable to differences in the distribution of asthma subtypes? The odds ratios in Table 2 need to be defined. I assume they represent the ratios of glioma odds but the word glioma does not appear in the title. Are the variables in Table 2 adjusted for age or not? The authors need to describe this (and they should adjust all their variables for age because we do not want to view results that

	are confounded by one of the strongest and most common confounders). It is no longer acceptable to put ** by significant p-values, especially when the odds ratios are not controlled for confounding and reflect sample size. This prohibition is based on the importance of the direction of odds ratios whether they are statistically significant. For example, what is the meaning of the small p-value for "undocumented" smoking exposure using community controls based on only four cases and not adjusted for confounding? Answer: None. Table 3 should have glioma in the title and if it is adjusted for potentially confounding variables, it should be so stated and the controlled variables should be included in the table footnotes. By the way, these odds ratios should be adjusted for confounding variables and the field has moved far-beyond the Greenland method of "variable selection", a paper which Greenland would presently disavow that was written in 1989. Table 4 is somewhat confusing because it suggests that Table 3 was not adjusted for confounding variables which would be a big mistake. In sum: 1. The authors misinterpret the atopy and glioma literature and do not realize that many of the studies included in the Amirian et al. study are much stronger than theirs and have much larger sample sizes. They need to study this literature if they are going to discuss it. 2. The authors do not analyze the data by asthma subtype (although I realize they do not have the sample size and perhaps the information). 3. The authors are probably not aware that the association between asthma and glioma (and other immune-related conditions) appears to change directions near the time of glioma diagnosis (Cahoon et al, British Journal of Cancer, 2014). I would therefore, exclude asthma information within two years before diagnosis (although they probably do not have an adequate number of observations to do so). 4. The authors have eliminated selection bias by using community controls (and probably induced it using MRI controls). Potential selection bias of hospital-based case-control studies of smoking and lung cancer was used by Berkson as a rationale to reject this association. He was wrong. 5. Are there are asthmatics who do not seek medical care? The authors need to address this issue.

REVIEWER	Quinn Ostrom Department of Medicine, Section of Epidemiology and Population Sciences Dan L Duncan Comprehensive Cancer Center, Baylor College of Medicine Houston, Texas, United States
REVIEW RETURNED	19-Sep-2018

GENERAL COMMENTS	The authors describe the results of a nested case-control study examining the association between glioma and asthma/atopic disease within the Rochester Epidemiology Project cohort using two sets of controls. This analysis attempts to eliminate the recall biases present in most other analyses examining the relationship between asthma and glioma by utilizing information recorded in the medical record prior to diagnosis with glioma. Additionally, the authors use two types of controls drawn from the same base population as cases (1- randomly sample match community controls, and 2- matched controls who have received MRI and found to not have a glioma). The manuscript is well written and the methods and data used are appropriate. In the introduction (page 6, lines 25-27) the authors describe the study done by Disney-Hogg et al as one comparing glioma SNPs with atopic disease, but this study is a mendelian randomization analysis that is meant to test the association between glioma and SNPs previously associated with atopic disease. Please rephrase. The sample size used for this analysis is small, and further discussion of whether it is sufficiently powered to detect an association with asthma would be appropriate. Within the methods section, the authors note that second hand smoke will be accounted for in the pediatric population. This analysis appears to focus on adult glioma. Could the authors please clarify the ages of individuals included in this analysis? The authors note that they did not find any association with atopic conditions other than asthma. While the exposure definition used for asthma seems appropriate, other atopic conditions may not necessarily be included in the medical record (e.g. seasonal or environmental allergies). This may limit the ability of this analysis to assess this association, as compared to studies that collect this data via patient self-report. eTable 1 should include Amirian, et al (reference 11). Additional comparison to prior studies should be incorporated into the discussion. The authors may also want to consider incorporating discussion of the following studies: 1. Amirian ES, Marquez-Do D, Bondy ML, Scheurer ME. Antihistamine use and immunoglobulin E levels in glioma risk and prognosis. Cancer Epidemiol. 2013. 2. Linos E, Raine T, Alonso A, Michaud D. Atopy and risk of brain tumors: a meta-analysis. J Natl Cancer Inst. 2007;99(20):1544-1550. 3. McCarthy BJ, Rankin K, Il'yasova D, et al. Assessment of type of allergy and antihistamine use in the development of glioma. Cancer Epidemiol Biomarkers Prev. 2011;20(2):370-378.

	4. McCarthy BJ, Rankin KM, Aldape K, et al. Risk factors for oligodendroglial tumors: a pooled international study. Neuro Oncol. 2011;13(2):242-250.7 5. Scheurer ME, Amirian ES, Davlin SL, Rice T, Wrensch M, Bondy ML. Effects of antihistamine and anti-inflammatory medication use on risk of specific glioma histologies. Int J Cancer. 2011;129(9):2290-2296. On Table 2, it would be easier to interpret p values as compared to odds ratios for demographic characteristics between cases and controls. Please also include p values on Table 3.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

1. The objective of this research is not clearly defined. Presumably the authors are studying the association between asthma and glioma yet they refer to the literature on atopy and glioma in their introduction. Contrary to the authors' statements in paragraph 2, page 6, the evidence for an association between atopy and glioma is consistent and strong. This is the reason that Amirian et al. were able to publish a paper entitled, "Approaching a Scientific Consensus on the Association between Allergies and Glioma Risk…", which is cited by the authors who write, "an inverse association between history of allergy and risk of glioma was found in the majority of studies". Their supplemental eTable 1 misrepresents the "majority of studies" on atopy and glioma because it is not complete. In summary, the authors misinterpret the atopy and glioma literature and do not realize that many of the studies included in the Amirian et al. study are much stronger than theirs and have much larger sample sizes. They need to study this literature if they are going to discuss it.

Response: We appreciate the reviewer's thoughtful and helpful comments. We provide our response to the reviewer comments in two parts: 1) our specific responses to the each of the reviewer's comments and 2) updated literature summary (including updated eTable 1). Briefly, our overall study results are consistent with the reviewer's interpretation of the literature (an inverse association between asthma and the risk of glioma). While our study results potentially support an inverse association between asthma and the risk of glioma of the literature, they provide a potential clue for why some of the literature on the association between asthma and the risk of glioma has been inconsistent by showing the role of detection bias in attenuating an inverse association. We believe these findings improve our current understanding of the relationship between asthma and the risk of glioma. We included the summary of the responses to the reviews in the revised manuscript.

1) Responses to the reviewer's specific comments

A. "The objective of this research is not clearly defined":
The main "objective" of our study was to address the methodological limitations of the previous studies which may obscure the true biological relationship between asthma (not atopy or overall allergic diseases) and the risk of glioma which could be a source of inconsistent study results as specifically summarized in the updated eTable 1 and the following section. For example, 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 can be possible

from subjects with subtle neurological impairment and their caregivers as some literature indicated), 2) detection bias(1-3) stemming from differential detection of outcome (or exposure) as a result of differential health care access between asthmatics and non-asthmatics as well as between glioma cases and controls. For example, asthmatics might be more likely to seek medical care and have a higher likelihood of raising neurological symptoms associated with glioma and undergoing imaging studies for the brain, than non-asthmatics. Similarly, glioma cases might be more likely to seek medical care and evaluation for their current or previous respiratory symptoms leading to an identification of asthma as an exposure in a form of Berkson bias (see our responses under section D below for details), and 3) heterogeneity of asthma as the emerging literature(4-9) considers asthma as a heterogeneous disease instead of a single entity (eg, as childhood asthma is more atopic whereas adult asthma is less atopic and thus, previous studies, that reported the inverse association between asthma and the risk of glioma, were predominantly adult studies. None of pediatric studies showed statistically significant inverse associations). All these concerns might contribute to the inconsistent study results and previous studies did not adequately address these limitations.

Thus, our study was specifically designed to address these limitations in investigating the association between asthma and the risk of glioma by using a better asthma ascertainment approach (i.e., asthma criteria) and different control sets. To highlight detection bias we updated Tables 2 and 3 by removing results of “combined controls” in the tables and manuscript as we found significantly different results between two different control sets.

B. “the evidence for an association between atopy and glioma is consistent and strong”: We concur with the reviewer’s interpretation of the literature suggesting strong evidence for an inverse association. Schwartzbaum et al did a cohort study (using 3 cohorts) by collecting history of allergies before they developed glioma to determine whether previous case-control findings of an inverse association of allergies and glioma would be replicated using a cohort design, but failed to report asthma separately due to too small a number of asthma cases among those who developed glioma later.(10) The purpose of our study is not “identifying the association” itself, rather is addressing the methodological issue including recall bias stemming from questionnaire which is administered several years after glioma diagnosis to sick patients or their proxies as well as detection bias potentially originated from controls who have different access to health care from cases. However, in the context of causality, which is the ultimate goal of the epidemiological studies guiding basic researchers to unravel the underlying mechanisms, the current literature is still subject to further investigation to establish the causal relationship between asthma and the risk of glioma. In the context of well-established heterogeneity of asthma(11), the current literature for asthma, regardless of areas of interest (eg, GWAS, environmental studies, clinical trials, etc.), focuses on better defining phenotype and identifying a specific subgroup of asthmatics with regard to the outcome or exposure of interest. As it has, almost all asthma literature regardless of its outcomes or exposure has some degree of inconsistency in the associations. From this standpoint, inconsistency in the literature pertaining to the association between asthma and the risk of glioma is rather realistic and may reflect biological heterogeneity of asthma (apart from methodological caveats) which poses a differential effect on the risk of glioma. Thus, future investigations should gear toward 1) better identifying and addressing the methodological limitations resulting in inconsistency of the association and 2) stratifying asthmatics in relation to the risk of glioma (eg, a specific subgroup of asthmatics posing the greatest protective effect on the risk of glioma) which helps basic researchers to unravel the underlying mechanisms and clinicians for stratification and prognostication. Despite the limited sample size, we tried to address this goal in our present work.

C. “Their supplemental eTable 1 misrepresents the “majority of studies” on atopy and glioma because it is not complete”: We updated the literature summary and eTable 1 as below. We appreciate the reviewer’s suggestions and apologize for not including all relevant literature.

D. “the authors misinterpret the atopy and glioma literature. Some studies are much stronger than theirs and have much larger sample sizes.”: While we acknowledge that the majority of previous studies showed an inverse association between atopy and risk of glioma, we respectfully disagree with the reviewer’s comments.

The primary aim of our study was assessing the impact of asthma on the risk of glioma, not about all atopic conditions or atopic status in relation to the risk of glioma. The literature on the association between asthma and the risk of glioma has been inconsistent as summarized in eTable 1 below (only less than half studies reported statistical significant inverse association between asthma and risk of glioma). While it includes large studies, inconsistency observed in the literature is not surprising rather expected given the vast asthma literature on the inconsistent relationship of asthma (as an exposure or outcome) with environmental(12, 13) and genetic factors(14-17) as well as even treatment outcomes in clinical trials(18, 19) . Based on the updated literature summary in eTable 1 and our interpretation, we do not believe we misconstrued the literature on the association between asthma and the risk of glioma. For the reviewer’s comment, ”Some studies are much stronger than theirs and have much larger sample sizes”, we acknowledge that despite a population-based study design, our study sample size is smaller than previous studies. The purpose of this study is rather addressing the methodological issue that we may be able to explain part of the reasons for inconsistent literature. Below is our study design which has important strengths overcoming the aforementioned limitations of previous studies.

First, all previous studies were based on self-report of asthma or ICD code which have been subject to significant ascertainment bias. For example, almost a quarter of caregivers whose children were admitted to the hospital with a diagnosis of asthma reported that their children did not have asthma.(20) Similarly, 7.5% of high schoolers who had recurrent asthma symptoms were not diagnosed with asthma.(21) This is true for adults.(22) Given the crucial impact of ascertaining exposure status in a case-control study, to address this limitation, our study ascertained asthma status (exposure) by predetermined asthma criteria based on comprehensive medical record review and is the only study based on validated asthma criteria not relying on self-report. The predetermined asthma criteria also allowed us to assess temporal relationship between onset and prognosis of asthma and the risk of glioma as well (eg, active [current] asthma vs. inactive asthma related with risk of glioma).

Second, to address detection bias which may potentially obscure the previously reported inverse association, we used two different controls (community controls and MRI controls) in the analysis. Despite three different sets of controls used in Il’yasova et al’s study (ie, sibling, friend, and clinic-based controls) for differentiating impact of gene and environment on the association between asthma and glioma, this approach was not designed for addressing detection bias. The cohort study by Schwartzbaum et al (using 3 cohorts) collected history of allergies via questionnaire before they developed glioma but failed to report asthma separately due to too small number of asthma cases among those who developed glioma later.(10) Therefore, our study was the only study which assessed the potential detection bias which might have attenuated or obscured the association between asthma and risk of glioma, especially an inverse association. For example, as patients with asthma might be more likely to seek medical care or evaluations and raise preceding symptoms for glioma such as headache or other neurological symptoms during those visits, asthmatic patients are more likely to undergo imaging studies and detect glioma. Alternatively, this differential detection of exposure status (asthma) might have occurred to cases and controls in the context of case-control study design in a form of Berkson bias (although not exactly the same as Berkson bias).

This potential detection bias might attenuate or obscure the biological association (eg, an inverse association that the reviewer points out) or mislead to a positive association. Indeed, our study results might potentially support the presence of detection bias in the analysis based on cases and community controls because an inverse association (active asthma and the risk of glioma) was much stronger in the comparison between cases and MRI controls (minimizing a detection bias) (ie, odds ratio of 0.4 in Table 3), while the association between cases and community controls showed statistically non-significant positive association (odds ratio of 1.1). As we stated in the manuscript, MRI controls seem to have similar access to health care to glioma cases when we compared socioeconomic status (eg, education, HOUSES) and health care quality (eg, seasonal flu vaccine) between cases and controls (Table 2). Thus, we could interpret the detection bias described above might have been reduced by using MRI controls, and could better detect a true biological association between asthma and glioma. Our study design (selecting controls from a less biased source population those who had undergone similar tests or detection methods) is based on approaches suggested by the epidemiological literature. (1-3) 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.

In summary, MRI controls may be more suitable than community controls to assess association between asthma and risk of glioma by minimizing detection bias.

Third, our study is the only study which specifically addressed heterogeneity of asthma in relation to the risk of glioma by using predetermined asthma criteria. Multiple previous studies reported heterogeneity of asthma by total duration of asthma and age at asthma onset using self-report with inconsistent results.(23-26) 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 ascertained by medical chart review, compared to non-asthmatics, but not inactive (past) asthma, was associated with reduced risk of glioma. 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.

Therefore, despite the smaller sample size, our study has important strengths which addressed the limitations of previous studies and provides new and complimentary information which improved our understanding on the relationship between asthma and the risk of glioma.

2) Updated literature summary

We appreciate the reviewer's comments and suggestions for additional references to be included in this manuscript. We apologize for not including additional relevant literature in the original manuscript. In this section, we updated the literature by including each paper in eTable 1 as well as the summary statement for the table. Again, we appreciate the reviewer's suggestions.

A. A total 18 original studies (including 2 pediatric studies) were identified that reported effect size of the association between asthma and glioma (see eTable 1). Majority of them were retrospective case-control studies by surveying patients or proxies to identify history of asthma among cases and controls (i.e., self-report for a history of asthma), except one retrospective cohort study following up US VA patients.
    a. 7 adult studies (#1-7 of eTable 1) showed statistically significant inverse association.(27-30)(26, 31, 32)
    b. 7 adult (#8-14) and 2 pediatric (#17-18) studies showed toward inverse association, but not statistically significant.(23, 33-39)
    c. 2 adult studies (#15-16) showed toward positive association (one statistically significant).(40, 41)

B. There are 9 other case-control studies and one cohort study that reported inverse association between allergies (e.g., any allergy or IgE) and glioma (with or without statistical significance) without reporting association with asthma separately.(10, 42-50)

C. There are 5 systematic review using meta-analysis on this issue. 2 review papers reported "allergies" as a whole not separating asthma from allergies,(51, 52) while the other 3 papers (#17-19) reported results of meta-analysis regarding asthma and glioma.(53-55) Although these three systematic review papers reported overall inverse association between asthma and glioma, they did not include all 18 papers (5, 7, or 9 papers, respectively) available as of Dec 2018 in their analyses.

D. Limitations of literature and efforts to overcome limitations
    a. History of asthma collected by survey (eg, recall bias): All case-control studies surveyed patients or proxies (if patients could not report due to death or being too sick to answer, or pediatric patients) to identify history of asthma (ie, self-report which is subject to recall bias because a subtle impairment of cognitive function might affect the validity of self-report). There were some studies to overcome this recall bias.
        - Schwartzbaum et al did a cohort study (using 3 cohorts) by collecting history of allergies via questionnaire before they developed glioma to determine whether previous case-control findings of an inverse association of allergies and glioma would be replicated using a cohort design, but failed to report asthma separately due to too small number of asthma cases among those who developed glioma later.(10) They concluded that there is no strong evidence against (and some for) the hypothesis that allergies reduce glioma risk despite an inverse association without statistical significance.
        - Cahoon et al used 4.5 million VA patients including 4,383 brain cancer cases (95% glioma) to assess association of asthma with development of brain cancer, and found there was a significant inverse association between asthma and risk of glioma only when they limited history of asthma developed more than 2 years prior to development of glioma. They obtained history of asthma from hospital discharge records of VA hospitals, suggesting potential missing of childhood asthma unless asthma was ongoing and severe enough to be documented during hospitalization.
        - Two other studies used SNPs previously associated with asthma as a surrogate marker for asthma to assess association with glioma.(34, 41) However, given limited contribution of asthma-related gene to asthma phenotype later in the literature (eg, sensitivity of all reported asthma genes for predicting asthma was only 35% as a whole, (56)), the SNPs-based asthma case may not fully address ascertainment bias. However, as summarized in the eTable1, ORMDL3, one of the

most consistently replicated asthma genes (17, 41, 56, 57), has been reported to increase the risk of glioma in the study by Dobbins et al.

- Turner in his review paper reporting association between history of allergies and cancer risk (including glioma) concluded that although results from retrospective studies have consistently reported strong, inverse associations between allergies and risk of glioma, results from studies with medical records defined allergy, or from prospectively designed studies, are less clear.(58)
- As almost all previous studies relied on self-report for asthma status, the index date of asthma (especially adult glioma patients who may have had childhood asthma with or without remission, might be difficult to recall exact age at asthma onset), is difficult to define causing a potentially unclear temporal relationship between index date of asthma and the development of glioma. In our study, Predetermined Asthma Criteria allows us to define index date of asthma, the earliest day when one met or fulfilled the criteria.

b. Heterogeneity of asthma (asthma severity or control status at the time of glioma diagnosis) might be inadequately addressed in previous studies: The current asthma literature suggests asthma is heterogeneous (heterogeneity of asthma) not a single disease entity.(4-9) Realistically speaking for applying the study findings on the association between asthma and the risk of glioma, the current literature does not provide much information which subgroup of asthmatics gain the greatest protective effect among all asthmatics which is the crucial information for basic research attempting to unravel the underlying mechanisms for the protective effect and clinical care for stratification and prognostication. In this respect, our study tried to address and we found that active asthma, especially those with poorly controlled asthma had the greatest protective effect, compared to non-asthmatics and inactive asthma (Table 3).

c. Different source populations of cases and controls (eg, susceptibility bias and detection bias): As majority of cases were identified from hospitals or cancer registries while controls were from more diverse sources such as same hospitals, population registries, electoral roll, or siblings/friends obscuring their source populations, this might be another potential source for inconsistent results regarding association between asthma and risk of glioma. On the other hand, as our study setting is self-contained and has comprehensive medical record linkage system for the almost entire Olmsted County, MN, population (95%) through the Rochester Epidemiology Project, our study identified and enrolled cases and controls from the same and well-defined source population.

    - For example, one study used three different control sets (ie, siblings, friends, and clinic-based controls) reporting two inverse association (sibling or friend controls) with one statistical significance (sibling) and one positive association (clinic-based controls) while authors mentioned that clinic-based controls generally better approximate the prevalence data for population-based groups.(59) The results of this study highlight a potential susceptibility bias depending on controls in which the result of a case-control study is susceptible to selection of controls.
    - Although they did not report asthma separately, Lachance et al's study included three case-control studies from 4 institutions to assess association of glioma (high-grade) with histories of allergies, and found inconsistent results (ie, two inverse associations and one no association), which may account in part for different control populations.(42) Mayo Clinic and Duke-University of Illinois enrolled controls from clinics while UCSF identified controls by using random digit dialing.

Again, the results of this study raise a potential susceptibility bias depending on controls.

- Further, despite this different population sources between cases and controls, none of studies attempted to address a potential detection bias stemming from differential detection of outcome events between cases and controls in a form of Berkson bias (eg, different access to health care between two groups). For example, as patients with asthma might be more likely to seek medical care or evaluations and raise preceding symptoms for glioma such as headache or other neurological symptoms during those visits, they are more likely to undergo imaging studies and detect glioma. This potential detection bias might potentially attenuate or obscure the previously reported inverse association or mislead to a positive association. Indeed, our study results support this possibility as described above.

2. Nonetheless, the topic of this manuscript is asthma and glioma, which differs from atopy and glioma. As the authors clearly know, there are several asthma subtypes which need to be separately evaluated to determine whether allergic asthma or asthma per se is associated with glioma. Because the authors do not distinguish among asthma subtypes, it is difficult to interpret their results. That is, are the differences between the two types of controls attributable to differences in the distribution of asthma subtypes? In summary, the authors do not analyze the data by asthma subtype (although I realize they do not have the sample size and perhaps the information).

Response: We appreciate the reviewer's thoughtful comments. As the reviewer pointed, we did not have lab data to assess asthma subtypes (eg, Th2 high or low and atopic asthma with allergen-specific IgE).Thus, we are not able to address reviewer's comment. However, we tried to stratify asthma with and without other atopic conditions (e.g., allergic rhinitis or eczema) as a surrogate marker for "atopic asthma" to see any different pattern in association with glioma. We could not find any difference in part due to limited sample size (see the table below). However, we tried to assess the role of asthma severity and control status in the risk of glioma. Despite the small sample size, active asthma or poorly controlled asthma was associated with the risk of glioma (see Table 3),

Asthma and Atopic Conditions	Case	MRI Control	Odds ratio (95% CI)	P=0.077
No Asthma	114 (84.4%)	99 (73.3%)	(ref)	(ref)
Asthma without Atopic Condition	9 (6.7%)	17 (12.6%)	0.4 (0.2, 1.1)	0.06
Asthma with Atopic Condition	12 (8.9%)	19 (14.1%)	0.5 (0.2, 1.2)	0.12

3. The authors are probably not aware that the association between asthma and glioma (and other immune-related conditions) appears to change directions near the time of glioma diagnosis (Cahoon et al, British Journal of Cancer, 2014). I would therefore, exclude asthma information within two years before diagnosis (although they probably do not have an adequate number of observations to do so).

Response: We included Cahoon et al's study in the eTable. We do recognize that previous studies excluded subjects whose asthma occurred within 2 years prior to the development of glioma. However, the current asthma literature suggests asthma as a chronic condition with genetic predisposition and related lung function and immune dysfunction even prior to clinical manifestation of asthma (60, 61), and our asthma ascertainment was based on predetermined asthma criteria, not relying on subjects' recall. Therefore, we believe this exclusion may not be necessary. To address reviewer's comment, we assessed the association of asthma and risk of glioma after excluding those with <2 years of latency in our study, and comparison with MRI controls loses statistical significance given smaller sample size

(i.e., 1 case and 5 MRI controls excluded) (OR [95%CI] for MRI controls: 0.56 [0.29-1.08]). We added this in the Result section.

4. The authors have eliminated selection bias by using community controls (and probably induced it using MRI controls). Potential selection bias of hospital-based case-control studies of smoking and lung cancer was used by Berkson as a rationale to reject this association. He was wrong.

Response: We appreciate the reviewer's comment. Please see our response to Reviewer one's first comment above. Briefly, although the bias we attempted to address is not exact Berkson bias, we tried to minimize selection bias stemming from using only hospital cases, by utilizing Rochester Epidemiology Project (REP) data linkage system encompassing medical records of almost all Olmsted County residents across two different institutions in our study setting for identifying both cases and controls from same population (not a sample) derived from the REP (MRI controls as well as community controls were identified from the REP).

As described above, the reason why we included MRI controls is to capture a detection bias as we believe MRI controls are likely to be more suitable and similar to glioma cases as both had an MRI. This approach in a case control study has been supported by the literature as discussed above. As an example, MRI controls had similar access to health care as glioma cases, compared to community controls (ie, minimizing detection bias) as shown in socioeconomic status and health care access to vaccination). We respectfully disagree with the reviewer's comment on "MRI controls induced bias" as there was not any evidence for inducing detection bias from MRI controls (rather minimizing it). We revised our manuscript to reflect this point.

5. Are there asthmatics who do not seek medical care? The authors need to address this issue.

Response: Our previous study from the same study setting showed non-differential access to health care between asthmatics and non-asthmatics. (62) In addition, we assessed 1) seasonal influenza vaccine status as a surrogate marker for health care access and 2) education and HOUSES as socioeconomic status in our study as shown in Table 2. We found that MRI controls have similar access to health care to those with cases, while community controls tend to have lower access to health care than cases, potentially leading to under-detection of asthma.

6. The odds ratios in Table 2 need to be defined. I assume they represent the ratios of glioma odds but the word glioma does not appear in the title. Are the variables in Table 2 adjusted for age or not? The authors need to describe this (and they should adjust all their variables for age because we do not want to view results that are confounded by one of the strongest and most common confounders).

Response: We appreciate the reviewer's comment. We used conditional logistic regression model, which matched age and sex for Tables 2 and 3. We clarified this in the Table and added "glioma" in the title of Tables 2 and 3.

7. It is no longer acceptable to put ** by significant p-values, especially when the odds ratios are not controlled for confounding and reflect sample size. This prohibition is based on the importance of the direction of odds ratios whether they are statistically significant. For example, what is the meaning of the small p-value for "undocumented" smoking exposure using community controls based on only four cases and not adjusted for confounding? Answer: None.

Response: While we provided asterisk marks (*, **) to improve readability, we removed asterisk marks and added p-values in the tables per the reviewer's suggestion. We also removed effect sizes for "undocumented (missing)" variables as meaning of those variables and their effect size are not clear. We appreciate the reviewer's suggestions.

8. Table 3 should have glioma in the title and if it is adjusted for potentially confounding variables, it should be so stated and the controlled variables should be included in the table footnotes. By the way, these odds ratios should be adjusted for confounding variables and the field has moved far-beyond the Greenland method of "variable selection", a paper which Greenland would presently disavow that was written in 1989.

Response: We added glioma in the title of the Table 3. We apologize for our editorial error. Tables 2 and 3 were presented by conditional logistic regression model matching age and gender. We acknowledge limitations of the Greenland method. To minimize the impact of confounders for the association between asthma and risk of glioma, in this revision, 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).(63) We updated Table 4 per this approach, and confirmed inverse association between asthma and risk of glioma. We updated the manuscript accordingly.

9. Table 4 is somewhat confusing because it suggests that Table 3 was not adjusted for confounding variables which would be a big mistake.

Response: Please see our response to reviewer's comment #8 above.

Reviewer2:

1. The authors describe the results of a nested case-control study examining the association between glioma and asthma/atopic disease within the Rochester Epidemiology Project cohort using two sets of controls. This analysis attempts to eliminate the recall biases present in most other analyses examining the relationship between asthma and glioma by utilizing information recorded in the medical record prior to diagnosis with glioma. Additionally, the authors use two types of controls drawn from the same base population as cases (1- randomly sample match community controls, and 2- matched controls who have received MRI and found to not have a glioma). The manuscript is well written and the methods and data used are appropriate.

Response: We appreciate reviewer's comment.

2. In the introduction (page 6, lines 25-27) the authors describe the study done by Disney-Hogg et al as one comparing glioma SNPs with atopic disease, but this study is a mendelian randomization analysis that is meant to test the association between glioma and SNPs previously associated with atopic disease. Please rephrase.

Response: We revised our manuscript responding to reviewers' comments. We clarified that this study focuses on asthma (not allergies overall, to reduce heterogeneity) in the Introduction and eTable 1.

3. The sample size used for this analysis is small, and further discussion of whether it is sufficiently powered to detect an association with asthma would be appropriate.

Response: We mentioned this in our limitation of Discussion.

4. Within the methods section, the authors note that second hand smoke will be accounted for in the pediatric population. This analysis appears to focus on adult glioma. Could the authors please clarify the ages of individuals included in this analysis?

Response: This study included both pediatric and adult cases. For clarifying this, we added number (%) of pediatric cases in the Result section (19 [14%]).

5. The authors note that they did not find any association with atopic conditions other than asthma. While the exposure definition used for asthma seems appropriate, other atopic conditions may not necessarily be included in the medical record (e.g. seasonal or environmental allergies). This may limit the ability of this analysis to assess this association, as compared to studies that collect this data via patient self-report.

Response: We appreciate the reviewer's comment. We agree that physician diagnosis alone for other allergic conditions, especially seasonal allergy may be not accurate enough to identify true cases. In this revision, we clarified that our study focuses on asthma only, and acknowledged this point as follows; "atopic conditions other than asthma were not associated with the risk of glioma presumably due to a small sample size and methodological limitation (eg, undetected allergic rhinitis which might be identified by self-report)."

6. eTable 1 should include Amirian, et al (reference 11). Additional comparison to prior studies should be incorporated into the discussion. The authors may also want to consider incorporating discussion of the following studies:

1. Amirian ES, Marquez-Do D, Bondy ML, Scheurer ME. Antihistamine use and immunoglobulin E levels in glioma risk and prognosis. Cancer Epidemiol. 2013.
2. Linos E, Raine T, Alonso A, Michaud D. Atopy and risk of brain tumors: a meta-analysis. J Natl Cancer Inst. 2007;99(20):1544-1550.
3. McCarthy BJ, Rankin K, Il'yasova D, et al. Assessment of type of allergy and antihistamine use in the development of glioma. Cancer Epidemiol Biomarkers Prev. 2011;20(2):370-378.
4. McCarthy BJ, Rankin KM, Aldape K, et al. Risk factors for oligodendroglial tumors: a pooled international study. Neuro Oncol. 2011;13(2):242-250.7
5. Scheurer ME, Amirian ES, Davlin SL, Rice T, Wrensch M, Bondy ML. Effects of antihistamine and anti-inflammatory medication use on risk of specific glioma histologies. Int J Cancer. 2011;129(9):2290-2296.

Response: As we clarified above, our study focused on asthma (not allergies overall nor asthma medication) related to glioma. Therefore, we included only the suggested references pertaining to asthma (Linos's et al (2007), McCarthy et al (2011)) in eTable 1. But we cited all suggested references in the Manuscript (see Discussion).

7. On Table 2, it would be easier to interpret p values as compared to odds ratios for demographic characteristics between cases and controls. Please also include p values on Table 3.

Response: We updated Tables 2 and 3 by adding p-values.

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(30)	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(27)	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(28)	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(29)	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(26)	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(31)	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)	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.

					b. Low grade: 0.89 (0.58-1.37) (adjusted for education)	
7.Brenner et al, USA, 2002(32)	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(33)	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(34)	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(35)	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,	The adjusted odds ratios did not reveal any statistical significant associations between asthma and the occurrence of glioma with

					smoking history, and age at diagnosis)	yet pointing towards an inverse association.
11. Pouchieu et al, France, 2018(23)	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.Schlehofer et al, 6 countries (Australia, Canada, France, Germany, Sweden, and USA), 1999(36)	International population-based case-control study	-Cases:1,178 (hospitals or cancer registries) -Controls: 1,987 (population-based controls using different methods depending on each center) -Adults only	Histologically confirmed glioma	Survey: history of asthma	RR (95%CI): 0.75 (0.55-1.03)	There was a statistically significant inverse association between glioma and asthma.
13. Cahoon et al, USA, 2014(64)	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 (37)	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(40)	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(41)	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(38)	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, Denmark, Norway, Sweden,	Population-based case control study (CEFALO)	-Cases: 352 (cancer registries) -Controls: 646 (population registries) -Children only	Histologically confirmed glioma or through unequivocal	Survey: parent's report for child's history of asthma	aOR (95%CI) -Overall: 0.99 (0.54-1.82) -Current: 0.97 (0.42-2.25)	There was no association between asthma and risk of glioma.

and Switzerland, 2014(39)			diagnostic imaging		-Past: 0.80 (0.36-2.22) (adjusted for living on a farm before age 6 and socioeconomic status)	
C. Systematic review and meta-analysis						
Author	Study design	Study subjects	Conclusion			
19.Zhang et al, 2017(65)	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(54)	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(66)	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)			

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VERSION 2 – REVIEW

REVIEWER	Quinn Ostrom Baylor College of Medicine, Houston, Texas, United States
REVIEW RETURNED	15-Apr-2019

GENERAL COMMENTS	The revised manuscript is acceptable