

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. Schlehofer	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 boards) -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

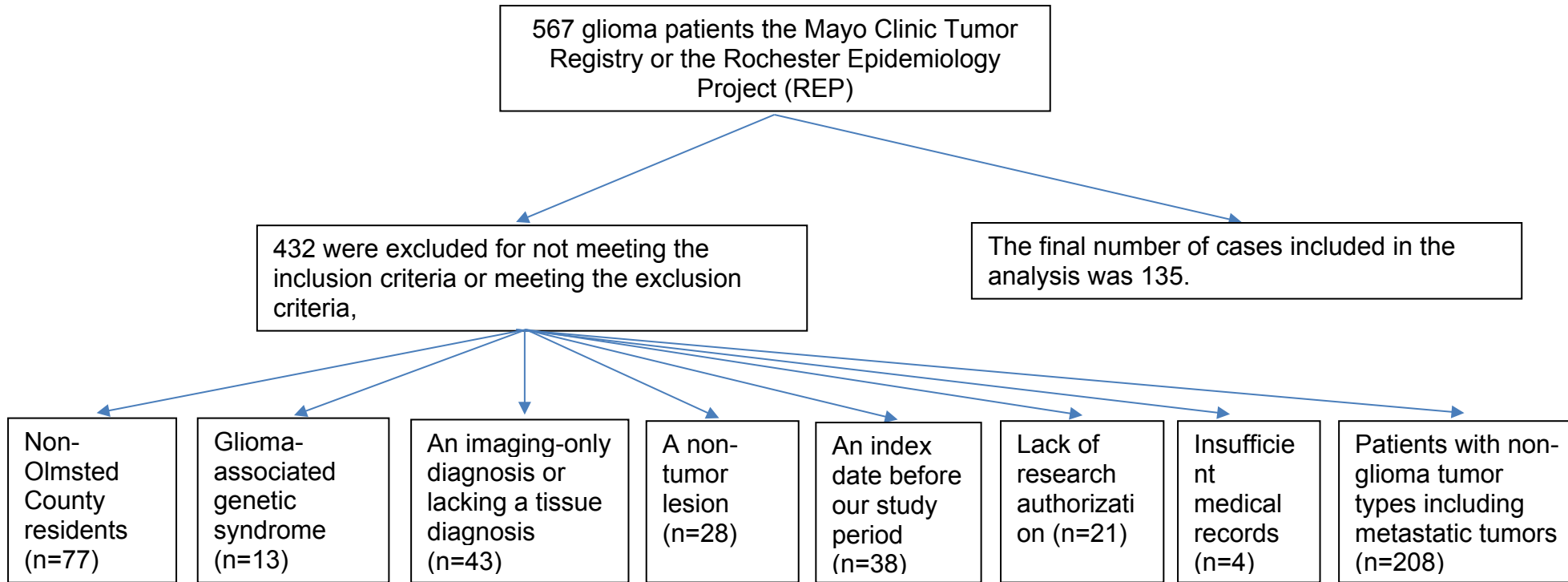
Denmark, Norway, Sweden, and Switzerland, 2014(18)	based case control study (CEFALO)	registries) -Controls: 646 (population registries) -Children only	confirmed glioma or through unequivocal diagnostic imaging	report for child's history of asthma	-Overall: 0.99 (0.54-1.82) -Current: 0.97 (0.42-2.25) -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, <i>P</i> < 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, <i>P</i> <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, <i>P</i> <.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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