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Title: Antidepressant drugs and risk of developing glioma: a national registry-based case control study and a meta-analysis

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Abstract

The aim of the present study was to investigate if use of antidepressants is related to the risk of developing lower (WHO grade 2-3) and higher grade (WHO grade 4) glioma. A registry-based case-control study was performed using 1283 glioma cases and 6400 age-, sex- and geographically matched controls, diagnosed in Sweden 2009-2013. Conditional logistic regression was used to analyze whether Selective Serotonin Reuptake Inhibitors (SSRIs) or non-SSRIs were associated with the risk of developing lower- or higher-grade glioma in the study population. Our results show that use of antidepressant medication was not associated with the risk of developing glioma. We also performed a meta-analysis in which the dataset from the present study was combined with results from two previous epidemiological studies to answer the same questions. The meta-analysis showed a modest risk reduction of developing glioma in relation to antidepressant treatment (OR 0.90 [95% CI 0.83-0.97]), when all glioma subgroups and all forms of antidepressant medications were combined. In conclusion, it remains possible that antidepressants may have common monoaminergic mechanism(s) that reduce the risk of developing glioma.

Abbreviations: AD=Antidepressants; HGG=High grade glioma; LGG=Low grade glioma, SSRI= Selective Serotonin Reuptake Inhibitor, TCA= Tricyclic antidepressant; ATC= Anatomical Theurapeutic Chemical; DRG= Diagnose Related Groups; ICD= International Classification of Disease

Malignant gliomas are a complex and heterogenous group of deadly brain tumors that differ vastly in aspects such as histological grade of malignancy, molecular subgrouping, and metabolic patterns (1). The clinical significance of these differences in, for example prognosis of the disease is highlighted by the increasing integration of these aspects in the recent WHO classifications of 2016 and 2021 (2, 3). The heterogenic profiles and development of gliomas are mediated in part by interactions with the tumor microenvironment (4). One aspect of this microenvironment that has been subject of increasing research interest is the role of monoaminergic transmissions (5, 6)

Depression and antidepressant medication is common in the general population and may be even more common amongst patients with glioma (7, 8). Such treatments are largely based on the catecholamine hypothesis of depression in that all established forms of pharmacotherapy for depression target monoaminergic transmission in general and serotonergic transmission in particular (9,10). As a consequence, the possibility has been raised that all, or some, of these drugs may influence the incidence and early development of gliomas. Either directly, by global effects on monoaminergic transmission that all antidepressants have in common (5, 11) or through unique mechanisms that may be specific to individual drugs (12-14).

The first relevant epidemiological study to investigate the risk of glioma in relation to depression and its treatment (15) used a sample of 773 patients with glioma and 1502 population-based controls and found that use of Tricyclic antidepressants (TCAs) was inversely associated with the risk of developing glioma, in a time and dose dependent manner. In a larger follow up study (16) including 3767 patients with glioma and 75340 population-based controls, a similar trend towards decreased risk for glioma associated with TCA was found. In this study the trend was, however, not statistically significant. Selective serotonin reuptake inhibitors (SSRIs) were not significantly associated with the risk of developing glioma in any of the studies. A meta-analysis of these previous two studies has been performed and showed that use of antidepressants was associated with a reduced risk of glioma, when all groups of antidepressant medications and all glioma grades (2-4) were entered in one analysis (7). However, questions regarding specific associations of non-SSRI:s/TCA or other possible more specific relationships in subgroups of patients with glioma was not addressed in the metanalysis. One possible interpretation of existing data may thus be that associations are global and related to monoaminergic dimensions of the brain biochemical environment. However, the extent to which such observations generalize across

study settings and whether they are specific to certain tumor grades or different classes of pharmacological substances still remains obscure.

In order to address this issue, we here report further data derived from Swedish national population-based registers on association between use of antidepressant medications and glioma incidence and furthermore, add this new data to a new meta-analysis.

Method

RISK North Database

All data used in this study was obtained from the RISK North Database which links data emanating from National Cancer Quality Registers to demographic and health care registries by using the unique personal identity number that every Swedish citizen possess (17). In the present study data from the following registries were used: National Quality Register for Brain Tumors, the Total Population Register, the Swedish inpatient register, the Swedish Cancer Register, and the Swedish Prescribed Drug Register. The national quality register for brain tumors is a database containing clinical data on brain tumor patients and is a collaboration between different healthcare regions in Sweden. The completeness of registration for the National Quality Register for Brain Tumors varied significantly between the six different healthcare regions in the country (18, 19). Only regions with a sufficient registration rate for new cases (≥97%) were included in the RISK North database. The regions that met this requirement were northern-, middle-, and south-eastern regions and the Stockholm-Gotland region. Coverage was validated through comparison with data in the Swedish Cancer Register to which all cancer cases are to be reported by legal mandate, but which does not contain clinical information other than diagnosis. In investigations of differences in risk of developing glioma in northern and southern regions of the country, all non-northern regions were considered southern regions.

Cases derived from the database included 1283 patients with glioma (WHO grade 2-4) diagnosed between 2009 and 2013 and were according to the construction of the RISK North database originally identified from the National Quality Registry for Brain Tumors. Included patients were above the age of 18, had a histologically verified glioma diagnosis, and consented to registration in the National Quality Register for Brain tumors. No exclusion criteria were used. Data regarding these patients histologically identified WHO glioma-grade was also extracted from the National Quality Registry for Brain Tumors. The RISK North database also includes 5 population-based controls for each case derived from the Swedish

Population Register. Controls derived from the database in the present study included 6400 individuals without a glioma diagnosis. Controls were matched to cases with regards to age, sex and geographical region at the time of the glioma diagnosis of the index case (matched on calendar time). Information about age and sex of the patients as well as controls was gathered from the Swedish Population registrer from Statistics Sweden. Since age and sex are (besides exposure to ionizing radiation) the only well-established and common epidemiological factors related to development of glioma, matching on further variables was not considered relevant. (20) For three glioma cases, matching to 5 controls was not successful and these cases were thus excluded from further analyses. (These patients are included in the descriptive data but not the case control analyses below.) Data on the prescription of antidepressants for both cases and controls were collected from the Swedish Prescribed Drug Registry, which covers approximately 99% of drug prescriptions made in Sweden (21, 22), from its start in 2005 to 2013. Information regarding depression diagnosis was gathered from the Swedish inpatient register from 2009.

This information was used to investigate if antidepressants, separated into SSRI and non-SSRI, were associated with the risk of developing higher grade (WHO grade 4) or lower grade (WHO grade 2-3) glioma. A separate sub analysis was made for TCA. Considering that there is evidence suggesting there may be geographical disparities in cancer incidence in Sweden (23), we also investigated if there was a difference in risk of developing higher-or lower-grade gliomas between northern or southern parts of the country. Lastly meta-analyses of antidepressants and the risk of glioma were performed.

Antidepressant exposure

Depression itself can sometimes be a presenting symptom of glioma (24) therefore, patients that were prescribed antidepressants before glioma diagnosis may in some cases already have pre-diagnosis symptoms of glioma. We attempted to eliminate this issue by defining exposure to antidepressants in both cases and controls as at least one prescription of antidepressants made from the start of the Swedish Prescribed Drug registry in 2005 up to one year before glioma diagnosis. For controls the same principle but also method was used, for assessment of, exposure to antidepressant medication. For depression and/or anxiety diagnosis the same buffer was used as for medication that is, we looked for instances of these diagnoses made > 1 year before the glioma diagnosis. Antidepressant exposure and risk of glioma were investigated for two main groups: SSRI and Non-SSRI. We did not exclude subjects from analyses based on exposure to other parallel prescriptions or conditions which for instance

means that subjects with multiple antidepressant medications (i.e. both SSRI and non-SSRI) will cause an overlap between groups. Similarly, controls for one type of substance might have been exposed to other substances. Mean total length of prescriptions of SSRI in our material was 684.5 (SD) days for patients with glioma and 775.6 (SD) days for corresponding controls. Mean total length of prescriptions of non-SSRI in our material was 500.4 (SD) days for patients with glioma and 614.3 (SD) amongst corresponding controls.

Antidepressants and depression definitions

Antidepressants, or Anatomical therapeutical chemical (ATC) code N06A, were analyzed overall and divided into two main groups: SSRI and non-SSRI. The SSRI group included ATC N06AB. Non-SSRI, or remaining ATC N06A groups, included: N06AA non-selective monoamine reuptake inhibitors, N06AF monoamine oxidase inhibitors, non-selective, N06AG monoamine oxidase A inhibitors, and N06AX other antidepressants. A separate subgroup analysis was performed for tricyclic antidepressants (ATC N06AA). Distribution of antidepressants amongst patients with glioma and controls are presented in Web Table 1. Depression and or anxiety diagnosis included international classification of diseases (ICD-9 and 10) codes: F30 - F39, 296, 298, 300, 301, 302, and 311 as well as diagnose related groups (DRG) codes: T10, T12, T13, T15, T76, and T79.

Meta analysis

A meta-analysis on the risk of developing glioma associated with antidepressants was performed. A literature search was performed using the search words "(antidepressant) AND (glioma)" in the Web of Science, PubMed, and Cochrane databases from inception to May 2023. Citation lists of eligible studies were also searched. Title and abstract of the 403 results were searched yielding two previous studies that matched our research question, Walker *et al.* (15) and Pottegård *et al.* (16). Walker *et al* (15) found a significant reduction in risk of glioma related to TCA use but not for SSRI (OR 0.66 [95% CI 0.49-0.89] and OR 0.96 [95%CI 0.61-1.53] respectively). Pottegård *et al* (16) found a non-significant trend towards decreased risk for glioma related to TCA use but no trend for SSRI (OR 0.85 [95% CI 0.72-1.03] and OR 0.92 [95% CI 0.83-1.03] respectively). These two studies as well as our present study were included in the meta-analysis, see Web Table 2 for further characteristics of the studies. All studies included were considered to be of good quality when assessed according to the Newcastle-Ottawa Scale (24, 25) for case-control studies, see Web Table 3 for a detailed assessment of each study.

Four meta-analyses in total were performed. These meta-analyses used up to 10 sets of case-control data from the studies described, see Web Table 4 for further details. These sets of case-control data were gathered from analysis according to groups of antidepressants (TCA, SSRI, Non-SSRI) and type of glioma (higher-grade, lower-grade) when available. The first meta-analysis investigated the risk of developing glioma in relation to antidepressant use in 8 sets of case-control data which included all datasets from previous studies, as well as datasets investigating SSRI and Non-SSRI from the present study. The second and third meta-analyses investigated the risk of developing glioma in relation to SSRI and Non-SSRI use respectively. The fourth and last meta-analysis investigated TCA and risk of glioma. A meta-analysis investigating disparities for different tumor grades was not possible as one of the studies, Walker et al. (15), had not included tumor grade. The other study included, Pottegård et al. (16), had included tumor grade in subgroup analyses; however, this data was judged incomparable to the remaining data from the present study as these analyses included few patients and only long-term exposure to antidepressants (³ 3years).

Statistical analysis

Risk North: We used conditional logistic regression to analyze associations between glioma diagnosis, antidepressants (SSRI, Non-SSRI and a sub-analysis of TCA) and depression and/or anxiety without pharmaceutical treatment. The variables included in the conditional logistic regression were age, sex, geographical region as well as calendar time. Results were presented separately for lower-grade glioma (WHO grade 2-3) and higher-grade glioma (WHO grade 4) as well as for SSRI and Non-SSRI. A subgroup analysis was performed for TCA. Multivariable unconditional regression was used to test for differences between northern and southern regions of the country. All tests were two-sided and $p<0.05$ was deemed statistically significant. Statistical analyses were performed using R version 4.0.3.

Meta-analyses: The meta-analyses were performed in SPSS version 28.0 using pre-calculated odds ratio (OR) and 95% confidence interval (CI) for relevant case control comparisons in the two previous studies described above as well as the current study in a random-effects model using restricted maximum likelihood estimator. Effect sizes used in the meta-analyses were gathered from the natural logarithmic value of the odds ratio in each case-control dataset. The variances were obtained from the standard error which was calculated using the following formula: ((log upper limit of 95% CI of OR) – log(OR))/1.96, using the OR and 95% CI from each case-control dataset.

Ethics

This study was performed in line with the principles of the Declaration of Helsinki. The current study falls within the aims of the RISK North database approved by the Regional Board of Ethics in Umeå (2014/278-31).

Results

Descriptive results:

RISK North: A total of 1283 glioma cases and 6400 controls were included in our study. 792 (61.7%) of the glioma cases had higher grade glioma and 491 (38.3%) had lower grade glioma. 758 (59.1%) were male and 525 (40.9%) were female. Mean age in glioma cases was 58.40 (SD= 14.73). Further baseline characteristics for cases and control are shown in table 1.

RISK North: Antidepressants and risk of developing glioma:

Antidepressant treatment was not associated with an increased risk of developing glioma in our study 0.96 (0.81-1.14), see Web Table 5. In our dataset, 135 patients with glioma had received SSRI treatment. Among these, 83 patients developed higher-grade glioma and 52 lower-grade glioma. SSRI use was neither associated with the risk of developing higher grade (OR 0.97 [95% CI 0.76 – 1.25]) nor lower grade glioma (OR 0.99 [95% CI 0.72-1.36]), see table 2. The risk of developing higher grade glioma (*P*=0.99) or lower-grade glioma (*P*=1.0) in relation to SSRI use did not differ between northern or southern parts of the country.

Out of the 100 patients with glioma who had received non-SSRI treatment, 73 developed higher- grade glioma and 27 lower-grade glioma. Treatment with non-SSRI was neither associated with higher-grade glioma (OR 1.07 [95% CI 0.82-1.40]) nor with lower-grade glioma (OR 0.72 [95% CI 0.48-1.10]), see table 3. The risk of developing higher grade glioma (*P*=0.999) or lower grade glioma (*P*=0.97) in relation to non-SSRI use did not differ between northern or southern parts of the country. TCA was not associated with the risk of lower-grade glioma (OR 0.88 [95% CI 0.46-1.70]), nor higher grade glioma (OR1.22 [95% CI 0.82-1.82]), see Web Table 6 for more details.

Depression without pharmacological treatment and the risk of developing glioma

Among those patients who received a glioma diagnosis, 21 patients had a previous diagnosis of anxiety and/or depression without any history of treatment with antidepressants. In this

subgroup, 14 patients developed higher-grade gliomas and 7 lower-grade gliomas. Depression and/or anxiety diagnosis alone was not associated with developing neither higher-grade (OR 0.92 [95% CI 0.52-1.63]) nor lower grade glioma (OR 0.68 [95% CI 0.31-1.51]) compared to subjects who didn't have depression or had antidepressant treatment, see table 4. No difference between northern and southern part of Sweden was seen in developing lower (*P*=0.98) or higher grade (*P*= 1.0) glioma with respect to depression/anxiety diagnosis.

Meta Analysis

Antidepressants and risk of glioma: The meta-analysis showed an overall modest significant reduction in risk of glioma in relation to antidepressant use (OR 0.90 [95% CI 0.83-0.97]), see figure 1 for further details. Heterogeneity between the studies included in our meta-analysis was deemed low. (tau ^{2}= 0.00, I^2 =0% and *Q*= 8.07, *P*=0.33) and no publication bias was shown on Egger's regression test (*P*=0.57).

SSRI and risk of glioma: The meta-analysis of SSRI use and the risk of glioma showed no significant relationship (OR 0.94 [95% CI 0.85-1.03]), see figure 2. There was no heterogeneity between the studies (tau ^{2}= 0.00 I^2=0%, *Q*=0.29, *P*=0.96) and no publication bias according to Egger's regression (*P*=0.39).

Non-SSRI and risk of glioma: A moderate but non-significant trend was shown for non-SSRI use and the development of glioma (OR 0.83 [95% CI 0.68-1.01]) see figure 3. No significant publication bias was shown (Eggers regression *P*=0.89) and heterogeneity between the studies was moderate (tau ^{2}= 0.02 I^2=53%, *Q*=6.13 *P*=0.11).

TCA and risk of glioma: The meta-analysis of TCA use and risk of glioma showed no significant relationship (OR 0.86 [95% CI 0.67-1.10]) see figure 4 for further detail. There was a moderate heterogeneity between the studies (tau ^{2}= 0.03, I^2=54%, *Q*=5.87 *P*=0.12) and no publication bias (Egger's regression *P*=0.50)

Discussion

In this study no significant association between the use of antidepressants and glioma incidence was found in any of the subgroups. However, when our results were combined with data from two previous population-based studies and all antidepressants, and all tumor grades were analyzed together, use of antidepressants proved to be slightly (OR=0.90) but significantly protective against gliomas whereas associations for specific groups of antidepressants (SSRI vs non-SSRI) were still not found.

Several explanations for this global result and for the lack of associations in subgroup analyses are possible. First, the findings may be caused by pharmacodynamic mechanisms common to all or most antidepressant medications which would in such case most likely involve aspects of monoaminergic transmission. Second, the associations could be a result of methodological or statistical artifacts such as chance findings or confounding. This could be consistent with the fact that findings albeit significant were very modest in size. Finally, there is still a theoretical possibility that the observed association may be driven by mechanisms relevant only to a subset of pharmacological substances and/or tumor types since the subgroup analyses were underpowered to detect significant associations relative to the global analysis. The reason for this being that much of the data was not included in the metanalyses that took both tumor grade and type of medication into account.

Despite the long-standing hypothesis that protective outcome against gliomas may be specific to TCAs neither our study nor the comprehensive metanalysis presented here supports this notion. While a non-significant trend towards a decreased risk of glioma in non-SSRI and TCA users was observed in the meta-analyses, we noted moderate heterogeneity in glioma risk among studies. The inherent diversity within glioma subtypes and variations in follow-up duration may have contributed to this heterogeneity. Our findings show different risks associated with non-SSRI and TCA antidepressant use: a higher risk for higher-grade gliomas and a lower risk for lower-grade gliomas, albeit without statistical significance. However, in Pottegård's study (16), long-term use of TCA showed protective effects on higher grade glioma and astrocytoma (grades II-III) but not on Oligodendroglioma (grades II-III). This might be taken to suggest that the variability among glioma subtypes may have implications for the nature of associations between antidepressants and glioma risk. Larger studies with higher resolution with regard to tumor type and substance are needed to further establish whether such a relationship exists. Furthermore, the possibility of protective effects for specific substances such as fluoxetine (26) cannot be excluded based on the present data.

With regard to the negative association between antidepressants in general and gliomas described in the present metanalysis, there are possible mechanistic explanations that albeit

speculative may make biological sense. Perhaps most important amongst these is the fact that the mitochondrial enzyme MAOA which is involved in the degradation of monoamines including serotonin is inhibited by most antidepressant medications (27, 28). MAOA activity is an important source of brain oxidative stress (29), which could in turn be an important risk factor for the development of glioma (30). Consistent with this hypothesis several clinical studies have noted that antidepressant treatment is associated with decreased levels of oxidative stress (31-33).

It may also be noted that there are also possible points of interaction between monoaminergic transmission and gliomas that may be cause for caution in using antidepressant medications in this context. Most important here from a clinical point of view may be the influence of serotonin on angiogenesis (5). It might however be argued that such influences may primarily be relevant for the prognosis of existing gliomas rather than incidence of the disease. This might offer one possible explanation for the paradoxical observation that antidepressants are negatively associated with glioma incidence whereas use of antidepressants amongst patients with glioma appears to be negatively associated with survival. (34, 35)

The sample size and the national registry-based study design can be considered strengths of the present study. As mentioned in the introduction, our study was also the first of its kind to investigate higher- and lower-grade glioma separately. Furthermore, the fact that we were able to address the possibility of confounding by depression and/or anxiety by using prescriptions that began 1 year or more prior to index date allowed us to reduce the risk of protopathic bias. Lastly, our study included our data in meta-analyses and thus enabled investigation of global associations of antidepressants as well as those for specific subgroups.

Our study also has several important limitations to take into consideration. It did for example not account for dosage of antidepressants, time used or the possible confounding of the overlap between SSRI and Non-SSRI groups among exposed cases. (We chose not to exclude cases of overlap, for instance individuals who used both SSRI and non-SSRI from our analyses in the interest of retaining maximal power in our analyses.) Our study did furthermore not specifically adjust for level of depression and/or anxiety which has in previous studies been associated with decreased survival in patients with glioma and thereby possibly also glioma development (8,36,37). Furthermore, we did not specifically control for the fact that particularly tricyclics are sometimes prescribed for pain. We were able to study a subgroup of patients with a diagnosis of depression and/or anxiety without pharmacological treatment. (This group was, furthermore, in the interest of maximizing statistical power,

broadly defined.) However, the fact that we were unable to ascertain that these cases did not systematically differ from those treated pharmacologically (i.e., by being less severe), does unfortunately limit their value as controls.

Conclusions:

In sum, the data currently available which comprises 5 823 glioma cases and 83 242 population-based controls derived from Great Britain, Denmark and Sweden show a modest but significant negative association between antidepressant medication and incidence of gliomas. However, more specific associations, that may be unique to a specific subcategory of antidepressants or gliomas of a certain level of malignancy could not be demonstrated. One possible explanation for these findings could be that they mirror pharmacological mechanisms common to most or all antidepressants such as an alteration of the balance of monoaminergic neurotransmitters such as serotonin.

From a clinical point of view, the associations seen here are small and may not warrant changes in prescription practices of antidepressant medications.

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Table 1. Baseline characteristics of 1283 glioma cases and 6400 controls in Sweden 2009-2013

SSRI= Selective Serotonin Reuptake Inhibitor; TCA=tricyclic antidepressants; AD=antidepressant

	Glioma cases (n=1283)	Lower-grade glioma, WHO grade 2-3 (n=491)	Higher-grade glioma, WHO grade 4 (n=792)	Controls (n=6400)
Mean age (SD)	58.4 (SD=14.7)	51.3 (SD=16.3)	62.8 (SD=11.6)	58.4 (SD=14.7)
Gender				
Men (%)	758 (59.1%)	273 (55.6%)	485 (61.2%)	3780 (59.1%)
Women (%)	525 (40.9%)	218 (44.4%)	307 (38.8%)	2620 (40.9%)
AD treatment prior diagnosis (% of total)	194 (15.1%)	68 (13.8%)	126 (15.9%)	1000 (15.6%)
SSRI only (% of AD)	94 (48.5%)	41 (60.3%)	53 (42.1%)	473 (47.3%)
Non-SSRI only (% of AD)	59 (30.4%)	16 (23.5%)	43 (34.1%)	311 (31.1%)
SSRI and Non-SSRI (% of AD)	41 (21.1%)	11 (16.2%)	30 (23.8%)	216 (21.6%)
Depression without AD, (%)	21 (1.6%)	14 (2.9%)	7 (0.8%)	127 (2.0%)

Table 2.

The frequency of SSRI use in patients with lower grade (WHO 2-3) and higher grade (WHO 4) glioma and in matched controls in Sweden 2009-2013.

SSRI= Selective Serotonin Reuptake Inhibitor

	Lower grade glioma (%)	Matched Controls (%)	Odds Ratio (95% CI)
SSRI	52 (10.6%)	263 (10.8%)	0.99 (0.72-1.36)
No SSRI	439 (89.4%)	2177 (89.2%)	
	Higher grade glioma (%)	Matched Controls (%)	Odds Ratio (95% CI)
SSRI	83 (10.5%)	426 (10.8%)	0.97 (0.76 – 1.25)
No SSRI	709 (89.5%)	3534 (89.2%)	

Table 3.

The frequency of non-SSRI use in patients with lower grade (WHO 2-3) and higher grade (WHO 4) glioma and in matched controls. in Sweden 2009-2013.

SSRI= Selective Serotonin Reuptake Inhibitor

	Lower grade glioma (%)	Matched Controls (%)	Odds Ratio (95% CI)
Non-SSRI	27(5.5%)	183 (7.5%)	0.72 (0.48-1.10)
No non-SSRI	464 (94.5%)	2257 (92.5%)	
	Higher grade glioma (%)	Matched Controls (%)	Odds Ratio (95% CI)
Non-SSRI	73 (9.2%)	344 (8.7%)	1.07 (0.82-1.40)
No non-SSRI	719 (90.8%)	3616 (91.3%)	

Table 4. The frequency of anxiety/depression diagnosis without pharmacological treatment in patients with lower grade (WHO 2-3) and higher grade (WHO 4)glioma and in matched controls. in Sweden 2009-2013.

AD=Antidepressant

	Lower grade glioma (%)	Matched Controls (%)	Odds Ratio (95% CI)
Depression/anxiety without AD treatment	7 (1.4%)	51 (2.1%)	0.68 (0.31-1.51)
No depression/anxiety without AD treatment	484 (98.6%)	2389 (97.9%)	
	Higher grade glioma (%)	Matched Controls (%)	Odds Ratio (95% CI)
Depression/anxiety without AD treatment	14 (1.8%)	76 (1.9%)	0.92 (0.52-1.63)
No depression/anxiety without AD treatment	778 (98.2%)	3884 (98.1%)	

Figure 1.

Forest plot showing a meta-analysis of antidepressants and risk of developing glioma in epidemiological studies in United Kingdom, Denmark and Sweden published 2011-2023

HGG= higher-grade glioma; LGG=lower-grade glioma; SSRI= selective serotonin-reuptake inhibitor; TCA= tricyclic antidepressants

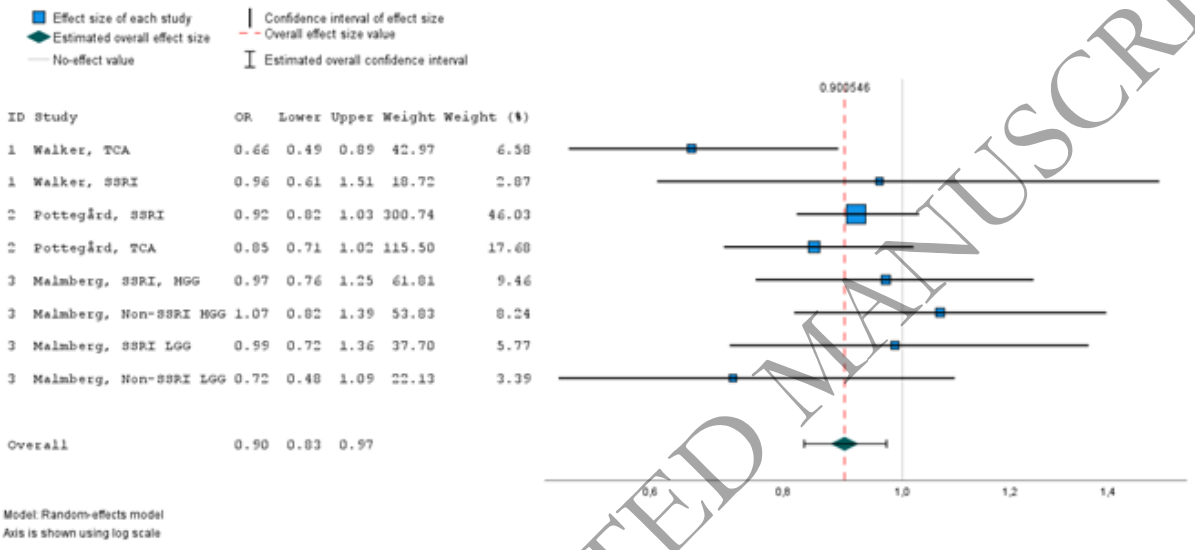

Figure 2.

Forest plot showing a meta-analysis of selective serotonin reuptake inhibitors and risk of developing glioma in epidemiological studies in United Kingdom, Denmark and Sweden published 2011-2023.

HGG= higher-grade glioma; LGG=lower-grade glioma; SSRI= selective serotonin-reuptake inhibitor;

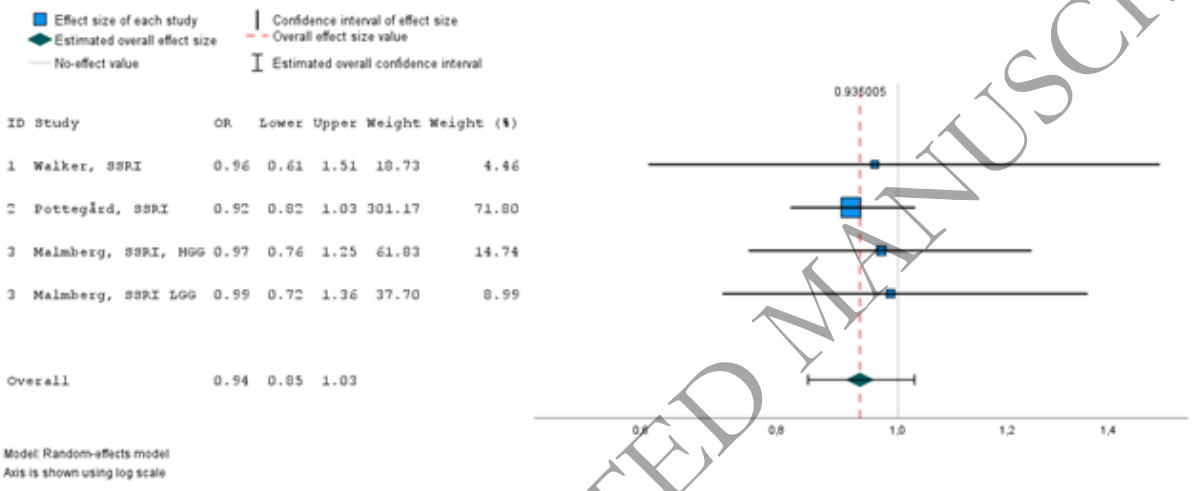

Figure 3.

Forest plot showing a meta-analysis of non-selective serotonin reuptake inhibitors antidepressants and risk of developing glioma in epidemiological studies in United Kingdom, Denmark and Sweden published 2011-2023.

HGG= higher-grade glioma; LGG=lower-grade glioma; SSRI= selective serotonin-reuptake inhibitor; TCA= tricyclic antidepressants

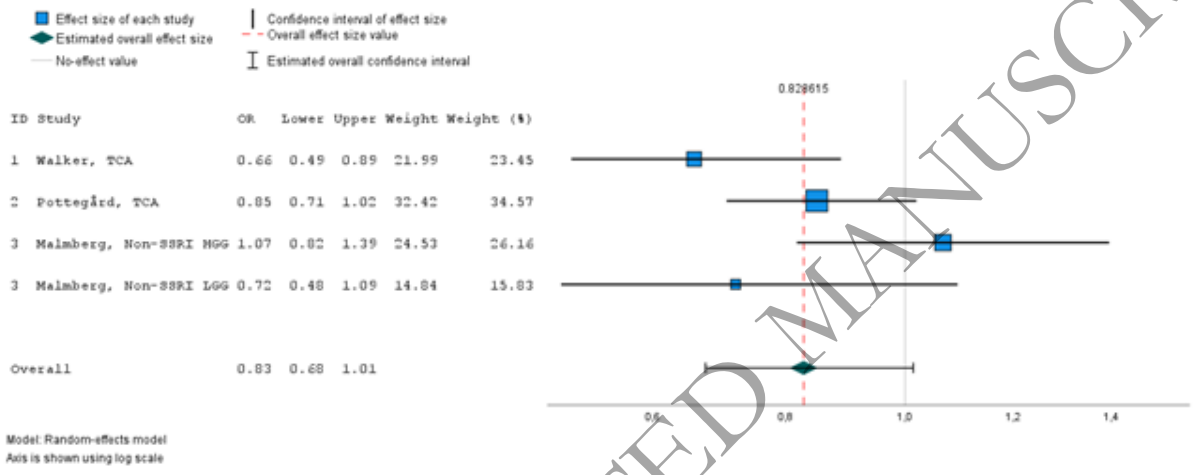

Figure 4.

Forest plot showing a meta-analysis of tricyclic antidepressants and risk of developing glioma in epidemiological studies in United Kingdom, Denmark and Sweden published 2011-2023. HGG= higher-grade glioma; LGG=lower-grade glioma; TCA= tricyclic antidepressants