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The impact of depression on risk of malignant glioma: A nationwide cohort study

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ABSTRACT

Background: Malignant glioma (MG) is a malignant brain tumor with a fatal prognosis. Depression is on the rise in society, and its negative association on prognosis of glioma patients is known. This study aimed to investigate the correlation between depression and MG risk by analyzing data from the Korean National Health Insurance System (NHIS).

Methods: A retrospective cohort study utilized NHIS data starting with 4,234,415 individuals aged 20 and above who had undergone health check-ups in 2009. Excluding 65,146 for cancer diagnosis, missing data, or a one-year lag period, 3,856,362 individuals were analyzed. Those diagnosed with depression per ICD-10 codes F32 or F33 before the check-ups formed the depression group, while the MG group was identified by ICD-10 code C71.

Results: Depression was found to have a significant association with glioma risk (hazard ratio 1.127, 95 % confidence interval 1.101–1.347), even with adjustment for age, sex, income, body-mass index (BMI), smoking, drinking, regular exercise, diabetes mellitus, hypertension and dyslipidemia. Furthermore, the severity of depression had a greater influence on MG incidence. Finally, subgroup analysis according to MG status revealed factors such as income, regular exercise, chronic kidney disease, and BMI to exhibit significant differences related to depression in the no-glioma group, but not in the glioma group.

Conclusions: These results suggest that depression may be associated with development of MG.

1. Introduction

The most common type of malignant brain tumor is glioma[1]. Despite extensive research efforts, the exact mechanisms and potential susceptibility factors for malignant glioma (MG) are not yet fully understood. Among the various suspected influences, the risk factor that has consistently been demonstrated to have an association with MG is exposure to ionized radiation[2,3].

According to an analysis of Global Burden of Disease study, depression exhibits a high prevalence worldwide and shows an increasing trend over time from 172 million to 258 million during about 30 years [4]. It particularly demonstrates a rising pattern among young adults, and the economic burden is also gradually increasing[5]. The onset of depression in MG patients is a negative factor that reduces survival outcomes and is a severe complication that decreases the quality of life [6,7]. However, depression diagnosis before or after surgery does not seem to affect the survival rate[7]. Some research confirms the impact of depression on cancer. One cohort study revealed that depression influences the occurrence of cancer in diabetes patients[8]. Furthermore, studies have confirmed an increased risk of various types of cancer, including lung, gastrointestinal, breast, urinary, and liver cancer, in patients having depressive disorder[9,10]. One possible explanation for depression as a risk factor for cancer is related to innate immune activation and inflammation[11]. In the context of MG, depression may not

Abbreviations: MG, Malignant glioma; NHIS, Korean National Health Insurance System; ICD, International Classification of Disease; DM, Diabetes mellitus; HTN, Hypertension; BMI, Body mass index; SD, Standard deviation (SD); CI, Confindence interval; HR, Hazard ratio; CKD, Chronic kidney disease; TNFa, Tumor necrosis factor-alpha; IL, Interleukin; VEGF, Vascular endothelial growth factor.

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simply be a comorbidity but could suggest a potential relationship with the disease entity itself.

This study analyzed the potential association between depression and MG risk in a large sample, using a nationwide Korean population database.

2. Methods and materials

2.1. Data source

This study utilized a retrospective, cohort design based on the Korean National Health Insurance System (NHIS) (Seong et al.,2017). The NHIS covers most of the Korean population, including citizens aged 40 and above and employed individuals aged 20 and above, which accounts for approximately 97 % of the population, totaling around 50 million people. The NHIS database includes clinical diagnosis, prescription drug data (including anticancer medications), and demographic information, as well as data on surgeries and radiotherapy. It also incorporates socio-behavioral history, such as weight, height, BMI, medical history, family history, smoking and drinking habits, and physical activity.

2.2. Study population

In 2009, a total of 4,234,415 individuals aged 20 and above who underwent health check-ups was sampled, representing 40 % of the population. After excluding 65,146 individuals diagnosed with any cancer (defined by International Classification of Disease, Tenth Revision [ICH-10] code C00–98) before the index date, as well as those with missing data of 277,860 individuals or a one-year lag period of 35,047 individuals, which excluded cases of expired or diagnosed as glioma within 1 year to reduce bias, the final study population consisted of 3,856,362 individuals. Among them, those diagnosed with ICD-10 code F32 or F33 within the five years before the health check-up were allocated to the depression group, which consisted of 3,574,324 individuals. Those without such diagnosis during that period were placed in the no depression group, which consisted of 282,038 individuals. The start date of the follow-up observation is the date of health screening, and the end date of the follow-up observation is the earliest date among the MG onset date, date of death, or December 31, 2020. The maximum follow-up observation period is 11 years, and the average follow-up observation period is 10.14 years. The diagnosis of MG was based on the ICD-10 code of C71. The No MG group included 3,852,612 individuals, while the MG group consisted of 3750 individuals.

2.3. Clinical variables

This study utilized NIHS data for analysis. Socio-behavioral data obtained through questionnaires were included. Both the health survey and the tests were conducted on the health screening date, which is the start date of the follow-up. Regarding smoking history, individuals who had smoked five packs or more in their lifetime and were still currently smoking were categorized as current smokers. Those who had smoked five packs or more but had quit smoking by the time of the questionnaire were categorized as ex-smokers, while those with a smoking history of five packs or less or no smoking history were classified as non-smokers. For drinking history, individuals who consumed 30 g or more of alcohol per day were designated as heavy drinkers, those who typically consumed less than 30 g of alcohol were categorized as mild drinkers, and those with no alcohol consumption history were labeled as non-drinkers. Age was determined based on the age at the time of the health examination. Regular exercise was defined as engaging in strenuous exercise at least three times a week, lasting for more than 20 min each time. Diabetes (DM) was defined as a fasting glucose level of 126 mg/dL or higher or use of insulin or oral hypoglycemic agents. Hypertension (HTN) was defined as a systolic blood pressure of 140 mmHg or higher and/or a diastolic blood pressure of 90 mmHg or higher or use of antihypertensive medication. Dyslipidemia was defined as a total cholesterol level of 240 mg/dL or higher or use of lipid-lowering medications. Body Mass Index (BMI) was calculated by dividing the square of height by weight. The severity of depression was defined for subgroup analysis. Severity stage 1 included individuals who were diagnosed with F32 or F33 within the five years before the health check-up but had no claims for the same diagnosis in the year of the health check-up on the basis of previous research that defined psychiatric disorders using a five-year medical history [12]. Severity stage 2 included those who were diagnosed with F32 or F33 within the five years before the health check-up and had claims for the same diagnosis in the year of the health check-up. This categorization distinguished between individuals with different levels of depression severity based on diagnostic history and claims for the year of the health check-up. The follow-up observation starts on the date of the health screening and ends on the earliest of the MG onset date, date of death, or December 31, 2020. The maximum follow-up period is 11 years, with an average of 10.14 years. Because the NHIS does not provide household income data, monthly health insurance premiums were used as a proxy for household income. Health insurance premiums are calculated differently depending on whether an individual is employee-insured or self-employed. For those who are employee-insured, premiums are solely based on individual wage income. For the self-employed, premiums are determined by both income and household property value including land and rental income. To categorize annual income levels, we used health insurance premiums divided into 20 quantiles, grouping them into four quartiles based on previous studies [13,14].

2.4. Statistical analysis

The baseline characteristics are presented as mean ± standard deviation (SD). For analysis of continuous variables, *t*-tests were used, while $\chi 2$ tests were employed for categorical variables. The incidence rate was calculated by dividing the number of cases by the total follow-up duration, and it was expressed per 1000 person-years. Cumulative incidence was analyzed using Kaplan-Meier analysis, and differences between groups were assessed using the log-rank test. To analyze the risk of glioma, a multivariable-adjusted Cox proportional hazards model was utilized, and hazard ratio (HR) and 95 % confidence interval (CI) were reported. Timescale was set as study on time. Model 1 was crude model and Model 2 was adjusted for age and sex. Model 3 included age, sex, income, BMI, smoking, drinking, regular exercise, DM, HTN, and hyperlipidemia. Subgroup analysis was conducted to examine the effects of gender and age, using Model 3. The proportional hazard assumption was evaluated using Schonfeld residual and log-log plots, and the analysis was conducted based on this assessment. In the subgroup analysis, factors affecting depression were compared by performing both univariate and multivariate analyses using logistic regression. Statistical analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), and a two-sided *p*-value <0.05 was considered statistically significant.

3. Result

Among the total patients, 282,038 had been diagnosed with depression, while 3,574,324 did not have depression. The mean age of depression group was 55.2 ± 13.4 years, which was older than no depression group at 46.4 ± 13.8 years ($p < 0.001$). The depression group also had a higher proportion of females (64.68 % vs. 43.68 %) ($p < 0.001$). For income distribution, 19.32 % of the depression group were in the lowest quartile (Q1) versus 19.44 % in the no depression group, 23.36 % in Q2 versus 19.49 %, 27.6 % in Q3 versus 25.53 %, and 29.55 % in Q4 versus 35.05 %. These differences were statistically significant ($p < 0.001$). In the depression group, the mean BMI was higher compared to the non-depression group, with values of 23.85 ± 3.21 and 23.69 ± 3.23 ($p < 0.001$). Individuals in the depression group smoked

Table 1
Baseline characteristics.

	No depression group (*n* = 3,574,324)	Depression group (*n* = 282,038)	P-value
Age, years	46.4 ± 13.8	55.2 ± 13.4	<0.001***
Sex, Male	2,012,912 (56.32)	99,624 (35.32)	<0.001***
Income			<0.001***
Medical aids	6179 (0.17)	1397 (0.5)	
Q1	690,416 (19.32)	54,826 (19.44)	
Q2	834,823 (23.36)	54,959 (19.49)	
Q3	986,523 (27.6)	71,998 (25.53)	
Q4	1,056,383 (29.55)	98,858 (35.05)	
Smoking			<0.001***
Non	2,084,690 (58.32)	206,350 (73.16)	
Ex	515,893 (14.43)	33,158 (11.76)	
Current	973,741 (27.24)	42,530 (15.08)	
Drinking			<0.001***
Non	1,780,334 (49.81)	195,075 (69.17)	
Mild	1,497,038 (41.88)	73,821 (26.17)	
Heavy	296,952 (8.31)	13,142 (4.66)	
Regular exercise	635,595 (17.78)	53,148 (18.84)	<0.001***
Diabetes mellitus	296,030 (8.28)	38,138 (13.52)	<0.001***
Hypertension	876,551 (24.52)	107,325 (38.05)	<0.001***
Dyslipidemia	616,041 (17.24)	80,489 (28.54)	<0.001***
CKD	234,499 (6.56)	29,747 (10.55)	<0.001***
Height, cm	164.2 ± 9.2	159.6 ± 8.9	<0.001***
Weight, kg	64.17 ± 11.69	60.94 ± 10.54	<0.001***
BMI, kg/m2	23.69 ± 3.23	23.85 ± 3.21	<0.001***

Medical aids: participants who received healthcare benefits under the Medical Care Assistance Act, Q1: quartile 1; the lowest category of income variability, Q2: quartile 2, Q3: quartile 3, Q4: quartile 4; the highest category of income variability, CKD: chronic kidney disease, BMI: body-mass index, n: number of patients, Mean ± standard deviation, Regular exercise was defined as intensive physical activity >3 days per week or moderate physical activity >5 days per week.

less than those in the non-depression group, with proportions of non-smokers at 73.16 % and 58.32 % ($p < 0.001$). In terms of alcohol consumption, the depression group had a lower proportion of drinkers compared to the non-depression group, with non-drinkers comprising 69.17 % and 49.81 %, respectively ($p < 0.0001$). For medical histories, the depression group exhibited a higher prevalence of history of HTN (38.05 % vs. 24.52 %), DM (13.52 % vs. 8.28 %), and dyslipidemia (28.54 % vs. 17.24 %) compared to the no depression group (all p < 0.001) (Table 1).

In the crude model, the HR was 1.753 (95 % CI: 1.588–1.935). After adjusting for age and sex in Model 2, the HR decreased to 1.225 (95 % CI: 1.108–1.355). Further adjustments in Model 3, which included income; BMI; smoking; drinking; exercise; and history of DM, HTN, or hyperlipidemia, resulted in an HR of 1.217 (95 % CI: 1.101–1.347) (Table 2). When analyzing the influence of the severity of depression, compared to stage 1, the HR increased in stage 2 from 1.646 (95 % CI: 1.457–1.860) to 1.965 (95 % CI: 1.682–2.296) in model 1, indicating a greater influence associated with more severe depression.

Subgroup analysis was conducted for gender and age, as described in Table 3. Baseline characteristics showed a difference in the occurrence of depression between genders, with a HR of 1.322 (95 % CI: 1.134–1.541) in male group and 1.149 (95 % CI: 1.007–1.313) in females ($p < 0.001$). However, the analysis conducted on MG patients did not reveal significant differences, with an HR of stage 1 being 1.258 (95 % CI: 1.040–1.522) in males and 1.137 (95 % CI: 0.969–1.336) in females ($p = 0.235$). Although depression patients showed a significant difference in age in baseline characteristics ($p < 0.001$), the analysis of MG patients did not indicate significant differences in depression risk across age groups. The HR were as follows - 1.354 (95 % CI: 0.794–2.308) for ages 20–39 years, 1.347 (95 % CI: 1.177–1.543) for ages 40–64 years, and 1.074 (95 % CI: 0.919–1.254) for ages over 65 years ($p = 0.065$), including severity ($p = 0.076$). In MG patients, gender and age may not significantly influence the relationship between depression and glioma risk.

From the baseline year of 2009 onward, the presence of depression was associated with a higher probability of MG diagnosis. Furthermore, considering the severity of depression, a trend was identified where the probability of MG diagnosis increased with higher severity (Fig. 1). This suggests that depression, especially in more severe forms, is associated with a higher likelihood of MG.

Additional analysis was conducted separately on patients with and without MG to determine whether other factors may relate to the presence of depression in one or both groups. For patients without MG, no significant differences were identified in relation to the presence or absence of prior depression, in line with the results from the overall cohort. However, in the MG group, this analysis revealed that some of the factors previously identified as having significant differences in relation to depression, such as income, smoking history, regular exercise, DM, HTN and chronic kidney disease (CKD), no longer maintained their statistical significance ($p = 0.876$, 0.532, 0.676, 0.143, 0.307, and 0.25, respectively). Body weight was found to differ significantly regardless of MG status, but the significance of BMI disappeared in the glioma group ($p < 0.001$ and $p = 0.447$) (Table 4). These results suggest that for patients with MG, other lifestyle and health factors may have a less pronounced or nonsignificant relationship with depression.

Table 2
Incidence rate and risk of malignant gliomas according to history of depression and its severity.

	Event	Duration, PY[†]	Incidence rate[‡]	HR (95 % CI)		
				Model 1 (Crude)	Model 2	Model 3
	Depression					
No (n = 3,574,324)	3303	36,312,084.07	0.091	1 (Ref.)	1 (Ref.)	1 (Ref.)
Yes (n = 282,038)	447	2,802,683.46	0.159	1.753 (1.588–1.935)	1.225 (1.108–1.355)	1.127 (1.101–1.347)
	Incidence rate according to severity					
No (n = 3,574,324)	3303	36,312,084.07	0.091	1 (Ref.)	1 (Ref.)	1 (Ref.)
Stage1 (*n* = 186,636)	280	1,867,449.95	0.150	1.646 (1.457–1.860)	1.191 (1.052–1.347)	1.187 (1.049–1.343)
Stage2 (*n* = 95,402)	167	935,233.5	0.179	1.965 (1.682–2.296)	1.288 (1.101–1.506)	1.273 (1.089–1.491)

Model 1: Non adjusted (Crude).
Model 2: Adjusted for age and sex.
Model 3: Adjusted for model 2 plus income, body-mass index, smoking, drinking, regular exercise, diabetes mellitus, hypertension and dyslipidemia.
Stage 1: who were diagnosed with F32 or F33 within the five years before the health check-up but had no claims for the same diagnosis in the year of the health check-up.
Stage 2: who were diagnosed with F32 or F33 within the five years before the health check-up and had claims for the same diagnosis in the year of the health check-up.
[†] Total follow up duration (person-year).
[‡] Per 1000 person-years. HR: hazard ratio, CI: confidence interval, n: number of patients.

Table 3
Subgroup analysis of risk of malignant glioma according to age and sex.

	Male					Female				
	Event	n	Duration, PY†	Incidence rate‡	HR (95 % CI)	Event	n	Duration, PY†	Incidence rate‡	HR (95 % CI)
		Depression ($p = 0.113$)								
No	2,012,912	1917	20,343,311.83	0.094	1	1,561,412	1386	15,968,772.23	0.087	1
Yes	99,624	182	966,122.5	0.188	1.322 (1.134–1.541)	182,414	265	1,836,560.96	0.144	1.149 (1.007–1.313)
		Risk of malignant glioma according to severity (p = 0.235)								
No	2,012,912	1917	20,343,311.83	0.094	1	1,561,412	1386	15,968,772.23	0.087	1
Stage1	66,699	113	652,976.04	0.173	1.258 (1.040–1.522)	119,937	167	1,214,473.92	0.138	1.137 (0.969–1.336)
Stage2	32,925	69	313,146.47	0.220	1.443 (1.134–1.838)	62,477	98	622,087.04	0.158	1.172 (0.954–1.439)

	Age 20–39 years					Age 40–64 years					Age ≥ 65 years				
	Event	n	Duration, PY†	Incidence rate‡	HR (95 % CI)	Event	n	Duration, PY†	Incidence rate‡	HR (95 % CI)	Event	n	Duration, PY†	Incidence rate‡	HR (95 % CI)
Depression (p = 0.065)															
No	1,180,438	369	12,147,463.9	0.030	1	1,981,927	1930	20,290,915.3	0.095	1	411,959	1004	3,873,704.86	0.259	1
Yes	33,756	14	346,238.89	0.040	1.354 (0.794–2.308)	171,973	241	1,755,808.93	0.137	1.347 (1.177–1.543)	76,309	192	700,635.63	0.274	1.074 (0.919–1.254)
Risk of malignant glioma according to severity (p = 0.076)															
No	1,180,438	369	12,147,463.9	0.030	1	1,981,927	1930	20,290,915.3	0.095	1	411,959	1004	3,873,704.86	0.259	1
Stage1	24,783	12	254,672.63	0.047	1.588 (0.894–2.824)	115,211	161	1180,350.28	0.136	1.355 (1.153–1.592)	46,642	107	432,427.04	0.247	0.972 (0.795–1.186)
Stage2	8973	2	91,566.26	0.022	0.717 (0.179–2.879)	56,762	80	575,458.66	0.139	1.334 (1.065–1.670)	29,667	85	268,208.59	0.317	1.238 (0.993–1.545)

p: p-value for interaction, n: number of patients.
† total follow up duration (person-year), ‡per 1000 person-years. HR: hazard ratio, CI: confidence interval.

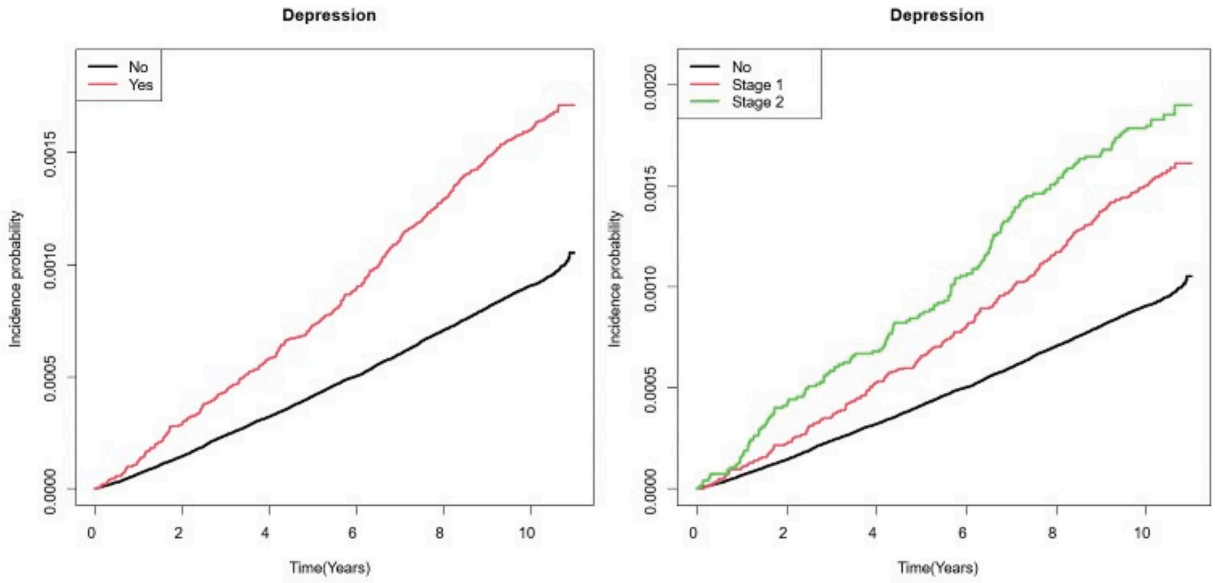

Fig. 1. Kaplan-Meier curve for depression in Malignant Glioma.
A Kaplan-Meier curve for the incidence of depression in malignant glioma, with a follow-up endpoint based on data from 2009. As the severity stage increases, the incidence probability of malignant glioma also rises.

4. Discussion

Approximately 15 % of all glioma patients have comorbid depression. However, investigations into factors such as gender, age, tumor size, and severity consistently failed to establish a clear association with depression[15]. It is well-known that the prevalence of depression is much higher in women than in men, with women having nearly twice the rate of depression[16]. However, the absence of this gender difference among patients who were diagnosed with both depression and MG in this study suggests a more direct relationship between MG and depression. While much has been discovered about depression occurring after the diagnosis of MG, this study represents the first analysis of the association between depression preceding MG diagnosis.

One of the major mechanisms underlying MG is chronic inflammation, which is known to induce DNA damage and promote tumor formation. Chronic inflammation, characterized by elevated levels of cytokines such as TNFa, IL-1, and IL-6, has been implicated in both depressive disorders and tumorigenesis (Grochans et al. 2022; Hoesel and Schmid 2013; Kim et al. 2004). TNFa, for example, can promote angiogenesis and suppress immune cell activity, which might contribute to tumor growth while also being linked to depression (Berthold-Losleben and Himmerich 2008; Uzzan and Azab 2021). Similarly, IL-1 and IL-6 are involved in both neuroinflammation and cancer development, with IL-1 influencing proangiogenic factors and IL-6 affecting the hypothalamic-pituitary-adrenal axis, potentially leading to depression (Goshen et al. 2008; Paugh et al. 2009; Ting et al. 2020). Moreover, one interesting finding in this study is that a longer duration of depression is positively associated with glioma development. Based on this finding, we suggest sustained neuroinflammation as a possible contributing factor to glioma development (Fig. 2), or conversely that glioma development may manifest as depression.

Given that this study does not directly assess the underlying mechanisms, other alternative hypothesis is that depression observed before MG diagnosis could be an early symptom of glioma rather than a cause. There is evidence suggesting that psychiatric symptoms, including depression, can precede the clinical detection of brain tumors, as seen in cases of frontal lobe glioma (Madhusoodanan et al. 2015; Nazlı Ş and Sevindik 2022). This raises the possibility that what was identified as depression in some patients might actually be an early manifestation of glioma.

Among the factors that were found to have a significant influence on the presence of depression, regular exercise, CKD, and BMI were not significant when limited to the MG group. For regular exercise, which are factors influenced by social effects, further experimental research may be necessary. Additionally, CKD often induces depression as it progresses to the terminal stage[17]. Given that MG is a fatal condition, it is conceivable that its relevance on depression is smaller when it is a result of chronic disease. The relationships between depression and BMI and obesity are well-established[18,19]. However, according to the results of this cohort, the effect of BMI is not significant when analyzed specifically for patients diagnosed with glioma[20,21]. Other studies show contradictory results, with some indicating that higher BMI is associated with a reduced risk of glioma[22]. Additionally, while BMI is positively associated with meningioma, the relationship with glioma is not clearly established[23,24]. However, according to another cohort study published in 2021, BMI had no association on incidence of MG, but waist circumference was found to be relevant in some glioma cases[25]. A more in-depth study on the relationship between BMI and neuroinflammation could potentially advance approaches to prevention and treatment for both depression and glioma.

In the glioma group, differences in depression related to socioeconomic factors, including regular exercise and income, disappear. This suggests a potential link between glioma depression that could offset the impact of these social factors. Previous studies have partially revealed a link between economic status and the incidence of glioma, indicating the need for further research on how depression interacts with these factors [26,27].

This study has several limitations. First of all, this study confirmed the potential influence of depression on MG, but it falls short of identifying a clear mechanism. Also, MG encompasses various subtypes based on origin cells and pathological findings, and this study did not differentiate between them, analyzing the entire MG population. The diagnosis of depression was based on healthcare data, which could lead to underreporting. Additionally, since the analysis was based on data from the NHIS in Korea, generalizing these results to the broader population is challenging, as they represent only the Korean insurance system. Studies indicate differences in the epidemiology and treatment outcomes of depression across different populations [28,29]. Thus, the study's limitation lies in its focus solely on Korean data. Information on the number of household members contributing to or relying on

Table 4
Factors affecting depression according to underlying malignant glioma.

	No glioma group (n = 3,852,612)					Glioma group (*n* = 3750)				
	No depression group	Depression group	P-value (Univariable)	Adjusted OR (95 % CI)	P-value (Multivariable)	No depression group	Depression group	P-value (Univariable)	Adjusted OR (95 % CI)	P-value (Multivariable)
Age, years	46.3 ± 13.8	55.2 ± 13.4	<0.001***	1.035 (1.034, 1.035)	<0.001***	56.3 ± 13.4	61.4 ± 10.8	<0.001***	1.023 (1.013, 1.032)	<0.001***
Sex, Male (%)	2,010,995 (56.31)	99,442 (35.31)	<0.001***	0.494 (0.488, 0.499)	<0.001***	1917 (58.04)	182 (40.72)	<0.001***	0.646 (0.492, 0.847)	0.002**
Income (%)			<0.001***		<0.001***			0.558		0.876
Medical aids	6164 (0.17)	1395 (0.5)		1		15 (0.45)	2 (0.45)		1	
Q1	689,752 (19.32)	54,749 (19.44)		0.438 (0.412, 0.466)		664 (20.1)	77 (17.23)		0.879 (0.189, 4.081)	
Q2	834,167 (23.36)	54,875 (19.49)		0.451 (0.412, 0.466)		656 (19.86)	84 (18.79)		0.980 (0.211, 4.551)	
Q3	985,645 (27.6)	71,874 (25.52)		0.478 (0.450, 0.508)		878 (26.58)	124 (27.74)		0.994 (0.215, 4.598)	
Q4	1,055,293 (29.55)	98,698 (35.05)		0.502 (0.472, 0.534)		1090 (33)	160 (35.79)		1.028 (0.223, 4.736)	
Smoking (%)			<0.001***		<0.001***			<0.001***		0.532
Non	2,082,768 (58.32)	206,034 (73.17)		1		1922 (58.19)	316 (70.69)		1	
Ex	515,374 (14.43)	33,102 (11.76)		1.170 (1.153, 1.188)		519 (15.71)	56 (12.53)		1.030 (0.719, 1.476)	
Current	972,879 (27.24)	42,455 (15.08)		1.030 (1.016, 1.045)		862 (26.1)	75 (16.78)		0.855 (0.614, 1.191)	
Drinking (%)			<0.001***		<0.001***			<0.001***		<0.001***
Non	1,778,430 (49.8)	194,736 (69.16)		1		1904 (57.64)	339 (75.84)		1	
Mild	1,495,879 (41.89)	73,735 (26.19)		0.784 (0.776, 0.792)		1159 (35.09)	86 (19.24)		0.587 (0.447, 0.769)	
Heavy	296,712 (8.31)	13,120 (4.66)		0.797 (0.783, 0.812)		240 (7.27)	22 (4.92)		0.762 (0.481, 1.209)	
Regular exercise (%)	634,937 (17.78)	53,057 (18.84)	<0.001***	1.048 (1.038, 1.059)	<0.001***	658 (19.92)	91 (20.36)	0.828	1.054 (0.823, 1.350)	0.676
Diabetes mellitus (%)	295,590 (8.28)	38,052 (13.51)	<0.001***	1.118 (1.104, 1.132)	<0.001***	440 (13.32)	86 (19.24)	<0.001***	1.227 (0.933, 1.613)	0.143
Hypertension (%)	875,257 (24.51)	107,095 (38.03)	<0.001***	1.197 (1.185, 1.208)	<0.001***	1294 (39.18)	230 (51.45)	<0.001***	1.125 (0.898, 1.409)	0.307
Dyslipidemia (%)	615,284 (17.23)	80,326 (28.53)	<0.001***	1.291 (1.279, 1.303)	<0.001***	757 (22.92)	163 (36.47)	<0.001***	1.258 (1.004, 1.576)	0.046*
CKD (%)	234,175 (6.56)	29,695 (10.55)	<0.001***	1.050 (1.036, 1.064)	<0.001***	324 (9.81)	52 (11.63)	0.228	0.822 (0.589, 1.148)	0.250
Height, cm	164.2 ± 9.2	159.6 ± 8.9	<0.001***			162.6 ± 9.1	159.3 ± 9.2	<0.001***		
Weight, kg	64.17 ± 11.69	60.94 ± 10.54	<0.001***			63.65 ± 10.74	61.38 ± 10.24	<0.001***		
BMI, kg/m2	23.69 ± 3.23	23.85 ± 3.21	<0.001***			24 ± 3.16	24.12 ± 3.05	0.447		

Medical aids: participants who received healthcare benefits under the Medical Care Assistance Act, Q1: quartile 1; the lowest category of income variability, Q2: quartile 2, Q3: quartile 3, Q4: quartile 4; the highest category of income variability, BMI: body-mass index, CKD: chronic kidney disease, n: number of patients, Mean ± standard deviation, OR: odds ratio, CI: confidence interval, Regular exercise was defined as intensive physical activity >3 days per week or moderate physical activity >5 days per week.

household income was unavailable. Additionally, income status based on insurance premiums did not accurately reflect actual individual income or account for multiple income changes. There is also a possibility of residual confounding, despite considering socioeconomic factors.

5. Conclusion

This nationwide population-based study revealed the correlation between depression severity and MG risk. The neuroinflammatory processes implicated in the onset of depression may have a connection to MG.

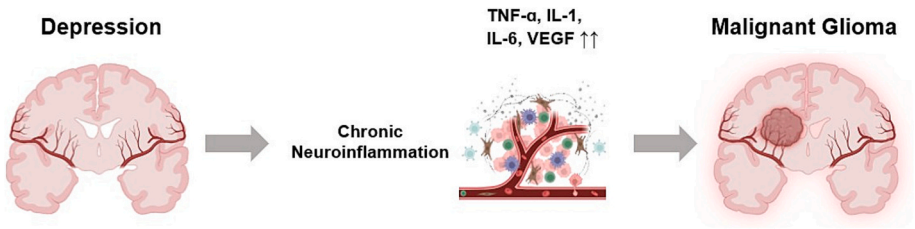

Fig. 2. A hypothetical model of the connection between depression and malignant glioma development via Neuroinflammatory Pathways. This diagram illustrates how chronic neuroinflammation, occurring during the progression of depression, may leads to an increase in key inflammatory mediators such as TNF-α, IL-1, IL-6, and VEGF. These cytokines, implicated in both depression and glioma pathogenesis, may drive DNA damage and contribute to tumor formation. By highlighting the potential biological mechanism linking prolonged depression to an increased risk of malignant glioma, the diagram emphasizes the role of chronic inflammation in facilitating this association.

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CRediT authorship contribution statement

Jin Eun: Writing – original draft, Visualization, Investigation. **Yoo Hyun Um:** Writing – review & editing, Visualization, Validation, Supervision. **Kyungdo Han:** Visualization, Software, Resources, Methodology, Formal analysis, Data curation. **Won-Il Joo:** Writing – review & editing, Supervision, Software, Resources. **Seung Ho Yang:** Writing – review & editing, Project administration, Methodology, Data curation, Conceptualization.

Declaration of competing interest

None.

Data availability

Upon request to the corresponding author, data sharing is possible.

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