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# Effect of the Interaction Between Depression and Sleep Disorders on Stroke Occurrence: A 17-Year Prospective Cohort Study in Korea

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**Objective** Previous studies have provided inconclusive results on the association between depression and stroke risk, and the potential modifying effect of comorbid insomnia on this association remains unclear. Our study aimed to clarify the independent roles of depression and insomnia as risk factors for stroke and to investigate the possibility of an interaction effect between these two conditions on stroke incidence.

**Methods** We used data from the Korean Genome and Epidemiology Study. The primary exposure was depression, measured by the Beck Depression Inventory. The secondary exposure was insomnia. The main outcome was the occurrence of stroke observed in biennial follow-up surveys. Cox proportional regression analysis was performed to estimate the effects of depression and insomnia on stroke incidence. We also conducted interaction analysis to investigate the interaction between depression and insomnia on stroke incidence.

**Results** During 16 years of follow-up involving 3,301 individuals, we documented 172 cases of new-onset stroke (4.3 cases per 1,000 person-years). Cox proportional logistic regression analysis showed that severe depression significantly increased the risk of stroke (hazard ratio [HR]: 2.06, 95% confidence interval [CI]: 1.13–3.75), whereas mild and moderate depression did not increase this risk. Interaction analysis demonstrated that stroke risk was increased with only moderate (HR: 2.04, 95% CI: 1.04–4.00) and severe (HR: 3.01, 95% CI: 1.43–6.31) depression among individuals without insomnia.

**Conclusion** Although general depression does not significantly increase stroke risk, moderate-to-severe depression may increase this risk, particularly in individuals without insomnia.

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**Keywords** Sleep disorder; Depression; Stroke; Risk factor.

## INTRODUCTION

Stroke is a major public health concern, causing significant morbidity and mortality worldwide. The World Health Organization reports that around 15 million people globally suffer from stroke each year.[1] Among them, around 5.8 million individuals succumb to the condition, thus positioning stroke as the second highest cause of death for individuals over 60 years of age.[2] The economic impact of stroke is also substantial, with its global costs projected to hit $34.4 billion by 2030. This figure includes direct healthcare expenditures, non-medical costs, and losses in productivity.[3] Identifying the modifiable risk factors of stroke is critical for developing effective preventive strategies and reducing its worldwide health burden.[4]

Depression is a widespread and incapacitating mental health condition, affecting over 264 million individuals globally.[5] Depression affects various physiological and pathophysiological mechanisms, suggesting its role as a potential risk factor for stroke.[6] Research indicates that depression can lead to alterations in the autonomic nervous system, increase inflammatory markers, and contribute to the dysfunction of the endothelial system, all of which are known to increase stroke risk.[7,8] Moreover, depression is associated with unhealthy lifestyle choices such as physical inactivity, poor diet, and smoking, which further exacerbate the risk of stroke.[9]

It is vital to investigate the effect of insomnia on stroke, especially considering its frequent co-occurrence with depression.[10] Research has shown that insomnia can independently increase stroke risk through mechanisms such as disrupted blood pressure regulation and increased inflammation.[11] The

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interplay between insomnia and depression may elevate this risk, underscoring the need to examine their combined effects on stroke susceptibility.

Previous research has not definitively demonstrated the association between depression and the incidence of stroke, and it is thought that this association may vary depending on the presence of insomnia, which often accompanies depression. Therefore, the aim of our study was to investigate whether depression and insomnia are independent risk factors for stroke and to determine whether there is an interaction effect between depression and insomnia on the occurrence of stroke.

## METHODS

### Study design, setting, and data sources

Our study was a prospective cohort study based on the Korean Genome and Epidemiology Study (KoGES), which is a population-based cohort study established in 2001 to examine genetic and environmental factors contributing to common, complex diseases in the Korean population. Our study primarily focused on chronic non-communicable diseases, including cardiovascular diseases, diabetes, and obesity. The methodologies, recruitment strategies, and baseline characteristics of the study participants have been previously described in detail in the literature. The KoGES comprises two independent prospective cohort studies in the cities of Ansung, a rural community, and Ansan, an urban community, based on the 2010 census data. These cohorts include Korean men and women aged 40−69 years, all of the same ethnicity. The sampling plan and selection criteria for these ongoing studies have been outlined in previous publications.

Between 2001 and 2002, a total of 7,129 and 10,957 eligible participants were identified in Ansung and Ansan, respectively. Of these participants, 5,018 participants (2,239 men and 2,779 women) from Ansung and 5,020 participants (2,523 men and 2,497 women) from Ansan completed the baseline examination. The participants have undergone biennial follow-up examinations, with the most recent being the 9th follow-up from 2019 to 2020.

Data collection was conducted through face-to-face interviews every 2 years by interviewers trained biennially using a standardized protocol. These interviews capture direct responses from the participants regarding various health factors, including smoking and alcohol consumption statuses.

### Study population and definition of stroke

Our analysis utilized data from the 2003−2004 survey of the KoGES, focusing on participants who completed the Beck Depression Inventory (BDI) and provided information on insomnia. We excluded participants with a physician-diagnosed stroke at the baseline to focus on new-onset strokes and avoid confounding effects, as a prior stroke could independently affect both depression and insomnia. Individuals with an unknown insomnia history were also excluded to ensure data accuracy, as insomnia is a key variable in our analysis, and including those with unknown histories could introduce bias, compromising the reliability of our findings. Additionally, participants with incomplete data or severe cognitive impairments were excluded to maintain data integrity and ensure accurate reporting of depressive symptoms and sleep disturbances, thereby ensuring a robust dataset for analyzing the interaction between depression, insomnia, and stroke risk.

Stroke cases were identified based on self-reported data from the subsequent 2005−2006 survey cycle. Participants who reported a stroke diagnosis after this period were classified as having experienced a stroke for the analysis.

### Depression and other risk factors

Participants completed an interviewer-administered questionnaire. The questionnaire administered in 2005−2006 collected information using the BDI, which is a widely used self-report questionnaire designed to assess the presence and severity of depressive symptoms. Depression was categorized based on the BDI scores. Participants were classified into 4 categories: no or slight depression (0−13), mild depression (14−19), moderate depression (20−28), and severe depression (29−63).[12] In the 2005−2006 questionnaire, we collected information on insomnia history by posing the following question: "Have you been diagnosed with insomnia by a physician?" We also collected information on demographic characteristics (age, sex, marital status, and education year), comorbidities (hypertension and diabetes mellitus), and health-related behavior (body mass index, smoking, alcohol intake, and physical activity). Additionally, we measured the serum levels of total cholesterol, triglycerides, and C-reactive protein.

### Statistical analysis

We calculated the descriptive statistics for the baseline characteristics of the study participants according to the depression category. The baseline characteristics of KoGES participants were compared using the Wilcoxon rank-sum test for continuous variables and the chi-square test for categorical variables. The crude 16-year (2005−2020) incidence rate of stroke was calculated as the number of at-risk cases per 1,000 person-years based on the presence of depression and insomnia. Subsequently, the hazard ratio (HR) and 95% confidence interval (CI) from Cox proportional hazards regression models with fixed covariates (with the group without depression as the reference group) were used to estimate the relative risk for the 15-year cumulative stroke incidence based on baseline

depression and insomnia. For our primary analysis using the Cox proportional hazards regression model, we assessed the proportional hazards assumption using Schoenfeld residuals. Diagnostic plots and tests confirmed that the assumption was met for the variables in the model. Multivariate logistic regression analysis was performed to estimate the effect of depression on the incidence of stroke after adjusting for potential confounders, which were selected based on their known associations with both depression and stroke, and tested using statistical criteria such as p-values and variance inflation factors to minimize bias and multicollinearity. Furthermore, we used the interaction term for depression and insomnia in the multivariate logistic regression model to estimate the effect of changes in depression on the study outcome according to the presence of insomnia. While interaction terms are valuable for exploring complex relationships, we provided a detailed interpretation of these interaction effects, discussing their implications for understanding the relationship between depression, insomnia, and stroke risk. We also considered potential reverse causation or bidirectional relationships between the study variables due to the observational nature of the study, acknowledging that depression and insomnia might influence stroke risk in a cyclical or reciprocal manner. We tested the multicollinearity among the covariates in the model and found no significant issues. All statistical analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA). This approach ensures transparency and robustness in our analysis, as we carefully adjusted for confounders and assessed the interaction effects and their implications comprehensively.

### Ethics approval

The study protocol was reviewed and approved by the Institutional Review Board of Chonnam National University Hospital (CNUH-2018-297).

## RESULTS

### Demographic findings

In comparison with the group without depression, the group with depression was older (53.7 years vs. 52.1 years) and had a significantly higher proportion of females (58.1% vs. 45.6%). The incidence of stroke was higher in the depression group (6.2% vs. 5.0%); however, this difference was not statistically significant. When depression severity was categorized as no depression, mild, moderate, and severe, a trend toward an increased incidence of stroke in the moderate and severe depression groups was observed; however, this trend did not reach statistical significance (p=0.04) (Table 1). Demographic analysis based on the presence of insomnia revealed a greater proportion of depression in the group with insomnia (mild: 12.5% vs. 9.0%; moderate: 6.6% vs. 4.2%; severe: 4.7% vs. 3.0%; p<0.01). The incidence of stroke was higher in the group without insomnia (5.3% vs. 5.0%); however, this difference was not statistically significant (Table 2).

### Main outcome

Cox proportional regression analysis was performed to assess the effect of risk factors on stroke incidence, which revealed that depression was not a significant risk factor for stroke (HR: 1.14, 95% CI: 0.85−1.51). Analysis of depression according to its severity demonstrated that mild and moderate depression did not significantly increase the risk of stroke; however, severe depression was associated with a significantly higher HR (2.06, 95% CI: 1.13−3.75) after adjusting for potential confounders using the group without depression as the reference. Additionally, insomnia did not significantly increase the risk of stroke (HR: 0.92, 95% CI: 0.67−1.27) (Table 3).

### Interaction outcome

Interaction analysis of the effects of depression and insomnia on stroke incidence indicated no significant interaction between depression and insomnia. However, when depression was categorized according to its severity, the results varied. In the group with insomnia, an increase in the severity of depression did not elevate the risk of stroke. Conversely, in the group without insomnia, a significant increase in stroke incidence was observed among participants with moderate depression (HR: 2.04, 95% CI: 1.04−4.00) and severe depression (HR: 3.01, 95% CI: 1.43−6.31) (p for interaction<0.01) (Table 4).

## DISCUSSION

In our study, only severe depression was identified as a significant risk factor for an increased likelihood of stroke. Notably, an elevated risk accompanied by depression was observed among participants without insomnia, where both moderate and severe depression significantly contributed to stroke risk. These findings underscore the importance of considering the severity of depression when evaluating stroke risk, particularly for individuals not affected by insomnia. The observation highlights a potential nuance in the interplay between mental health conditions and stroke, suggesting that the presence of insomnia might modulate the effect of depression on stroke risk. Our study results provide valuable insights for targeted interventions and patient management strategies.

Previous studies have reported an association between depression and an increased risk of stroke, suggesting various physiological and pathological mechanisms as potential me-

**Table 1.** Demographics of the study population according to the presence and category of depression

| Variables | All (N=3,301) | Depression | | p | Depression category | | | | p |
|---|---|---|---|---|---|---|---|---|---|
| | | No (N=2,669) | Yes (N=632) | | No (N=2,669) | Mild (N=340) | Moderate (N=171) | Severe (N=121) | |
| Age (yr) | 52.4±7.35 | 52.1±7.17 | 53.7±7.94 | <0.01 | 52.1±7.17 | 53.1±7.63 | 54.9±8.37 | 53.7±8.02 | <0.01 |
| Sex, female | 1,584 (48.0) | 1,217 (45.6) | 367 (58.1) | <0.01 | 1,217 (45.6) | 189 (55.6) | 108 (63.2) | 70 (57.9) | <0.01 |
| Married, yes | 3,046 (92.3) | 2,491 (93.3) | 555 (87.8) | <0.01 | 2,491 (93.3) | 305 (89.7) | 147 (86.0) | 103 (85.1) | <0.01 |
| Educational period >9 years | 2,125 (64.4) | 1,796 (67.3) | 329 (52.1) | <0.01 | 1,796 (67.3) | 188 (55.3) | 92 (53.8) | 49 (40.5) | <0.01 |
| Comorbidity | | | | | | | | | |
| Hypertension | 530 (16.1) | 424 (15.9) | 106 (16.8) | 0.59 | 424 (15.9) | 54 (15.9) | 32 (18.7) | 20 (16.5) | 0.81 |
| Diabetes mellitus | 208 (6.3) | 161 (6.0) | 47 (7.4) | 0.19 | 161 (6.0) | 31 (9.1) | 9 (5.3) | 7 (5.8) | 0.15 |
| Body mass index | | | | 0.06 | | | | | 0.05 |
| <18.5 (underweight) | 28 (0.8) | 20 (0.7) | 8 (1.3) | | 20 (0.7) | 5 (1.5) | 3 (1.8) | 0 (0.0) | |
| 18.5–24.9 (normal weight) | 1,859 (56.3) | 1,482 (55.5) | 377 (59.7) | | 1,482 (55.5) | 191 (56.2) | 106 (62.0) | 80 (66.1) | |
| >25.0 (overweight) | 1,414 (42.8) | 1,167 (43.7) | 247 (39.1) | | 1,167 (43.7) | 144 (42.4) | 62 (36.3) | 41 (33.9) | |
| Health-related behavior | | | | | | | | | |
| Alcohol intake, yes | 1,709 (51.8) | 1,386 (51.9) | 323 (51.1) | 0.71 | 1,386 (51.9) | 172 (50.6) | 85 (49.7) | 66 (54.5) | 0.83 |
| Smoking | | | | <0.01 | | | | | 0.02 |
| Current smoker | 577 (17.5) | 460 (17.2) | 117 (18.5) | | 460 (17.2) | 63 (18.5) | 32 (18.7) | 22 (18.2) | |
| Former smoker | 770 (23.3) | 659 (24.7) | 111 (17.6) | | 659 (24.7) | 65 (19.1) | 27 (15.8) | 19 (15.7) | |
| Never smoker | 1,954 (59.2) | 1,550 (58.1) | 404 (63.9) | | 1,550 (58.1) | 212 (62.4) | 112 (65.5) | 80 (66.1) | |
| Physical activity, vigorous | 1,669 (50.6) | 1,376 (51.6) | 293 (46.4) | 0.02 | 1,376 (51.6) | 164 (48.2) | 81 (47.4) | 48 (39.7) | 0.04 |
| Insomnia, yes | 1,234 (37.4) | 940 (35.2) | 294 (46.5) | <0.01 | 940 (35.2) | 154 (45.3) | 82 (48.0) | 58 (47.9) | <0.01 |
| Serum level of biomarker | | | | | | | | | |
| T-Ch (mg/dL) | 193 (172–217) | 193 (172–216) | 192 (174–218) | 0.14 | 193 (172–216) | 193 (173–219) | 190 (176–221) | 192 (172–211) | 0.42 |
| TG (mg/dL) | 114 (81–167) | 114 (80–167) | 115 (83–167) | <0.01 | 114 (80–167) | 114 (82–169) | 115 (85–167) | 117 (85–162) | 0.80 |
| CRP (mg/dL) | 0.64 (0.34–1.39) | 0.64 (0.34–1.37) | 0.65 (0.34–1.46) | 0.06 | 0.64 (0.34–1.37) | 0.68 (0.34–1.47) | 0.70 (0.34–1.74) | 0.58 (0.36–1.10) | 0.98 |
| Total stroke cases | 172 (5.2) | 133 (5.0) | 39 (6.2) | 0.23 | 133 (5.0) | 14 (4.1) | 13 (7.6) | 12 (9.9) | 0.04 |

Data are presented as mean±standard deviation, number (%), or median (q1–q3). T-Ch, total cholesterol; TG, triglycerides; CRP, C-reactive protein

**Table 2.** Demographics of the study population according to the presence of insomnia

| Variables | All (N=3,301) | Insomnia | | p |
|---|---|---|---|---|
| | | No (N=2,067) | Yes (N=1,234) | |
| Depression category | | | | <0.01 |
| No | 2,669 (80.9) | 1,729 (83.6) | 940 (76.2) | |
| Mild | 340 (10.3) | 186 (9.0) | 154 (12.5) | |
| Moderate | 171 (5.2) | 89 (4.3) | 82 (6.6) | |
| Severe | 121 (3.7) | 63 (3.0) | 58 (4.7) | |
| Age (yr) | 52.4±7.35 | 52.3±7.30 | 52.6±7.44 | 0.91 |
| Sex, female | 1,584 (48.0) | 882 (42.7) | 702 (56.9) | <0.01 |
| Married, yes | 3,046 (92.3) | 1,925 (93.1) | 1,121 (90.8) | 0.02 |
| Educational period >9 years | 2,125 (64.4) | 1,331 (64.4) | 794 (64.3) | 0.98 |
| Comorbidity | | | | |
| Hypertension | 530 (16.1) | 337 (16.3) | 193 (15.6) | 0.62 |
| Diabetes mellitus | 208 (6.3) | 133 (6.4) | 75 (6.1) | 0.68 |
| Body mass index | | | | 0.86 |
| <18.5 (underweight) | 28 (0.8) | 18 (0.9) | 10 (0.8) | |
| 18.5–24.9 (normal weight) | 1,859 (56.3) | 1,171 (56.7) | 688 (55.8) | |
| >25.0 (overweight) | 1,414 (42.8) | 878 (42.5) | 536 (43.4) | |
| Health-related behavior | | | | |
| Alcohol intake, yes | 1,709 (51.8) | 1,140 (55.2) | 569 (46.1) | <0.01 |
| Smoking | | | | <0.01 |
| Current smoker | 577 (17.5) | 395 (19.1) | 182 (14.7) | |
| Former smoker | 770 (23.3) | 531 (25.7) | 239 (19.4) | |
| Never smoker | 1,954 (59.2) | 1,141 (55.2) | 813 (65.9) | |
| Physical activity, vigorous | 1,669 (50.6) | 1,053 (50.9) | 616 (49.9) | 0.57 |
| Serum level of biomarker | | | | |
| T-Ch (mg/dL) | 193 (172–217) | 193 (172–215) | 194 (173–218) | 0.09 |
| TG (mg/dL) | 114 (81–167) | 114 (81–169) | 114 (79–162) | 0.20 |
| CRP (mg/dL) | 0.64 (0.34–1.39) | 0.66 (0.34–1.40) | 0.62 (0.33–1.39) | 0.23 |
| Total stroke cases | 172 (5.2) | 110 (5.3) | 62 (5.0) | 0.71 |

Data are presented as mean±standard deviation, number (%), or median (q1–q3). T-Ch, total cholesterol; TG, triglycerides; CRP, C-reactive protein

diators.[13,14] Depression can influence autonomic nervous system function, increase inflammatory responses, and lead to endothelial dysfunction, all of which are recognized risk factors for stroke.[7,15] This condition can also be linked to unhealthy lifestyle choices, such as decreased physical activity, poor dietary habits, and smoking, which can further amplify stroke risk.[16] These findings indicate potential pathways through which depression may elevate the risk of stroke. To the best of our knowledge, this research is the first to document the variance in stroke risk according to the severity of depression and thus adds a novel dimension to this field. Our findings revealed that while depression in general did not significantly increase stroke risk, severe depression was associated with a notable increase in stroke risk. Therefore, the severity of depression might differentially influence the risk of stroke, with severe depression possibly affecting more physiological and pathological pathways. Moreover, some studies suggest that depression and stroke may share common genetic risk factors, adding a layer of complexity to their relationship.[17] The genetic link demonstrates the interconnected nature of depression and stroke, emphasizing the importance of a nuanced approach to understanding and addressing the risk factors for these conditions.

Insomnia is recognized as a risk factor for several health conditions, including cardiovascular diseases, hypertension, diabetes, and mental health disorders.[18-20] In the case of stroke,

**Table 3.** Cox proportional logistic regression analysis of the study outcome

| Potential risk factors | Numbers at risk | Stroke events | PYS | Incidence rate per 1,000 PYS | Model 1 | Model 2 | Model 3 |
|---|---|---|---|---|---|---|---|
| | | | | | aHR (95% CI) | aHR (95% CI) | aHR (95% CI) |
| Depression | | | | | | | |
| No | 2,669 | 133 | 32,631.2 | 4.1 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| Yes | 632 | 39 | 7,341.0 | 5.3 | 1.19 (0.83–1.71) | 1.19 (0.83–1.71) | 1.14 (0.85–1.51) |
| Depression category | | | | | | | |
| No | 2,669 | 133 | 32,631.2 | 4.1 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| Mild | 340 | 14 | 4,032.8 | 3.5 | 0.81 (0.46–1.40) | 0.79 (0.45–1.36) | 0.77 (0.44–1.34) |
| Moderate | 171 | 13 | 1,948.9 | 6.7 | 1.38 (0.78–2.44) | 1.44 (0.81–2.56) | 1.41 (0.79–2.51) |
| Severe | 121 | 12 | 1,359.4 | 8.8 | 2.06 (1.14–3.72) | 2.06 (1.14–3.75) | 2.06 (1.13–3.75) |
| Insomnia | | | | | | | |
| No | 2,067 | 110 | 25,009.3 | 4.4 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| Yes | 1,234 | 62 | 14,962.8 | 4.1 | 1.08 (0.80–1.46) | 0.93 (0.68–1.27) | 0.92 (0.67–1.27) |

PYS, person-years; aHR, adjusted hazard ratio; CI, confidence interval

insomnia can exacerbate its risk through various mechanisms, such as increasing blood pressure, promoting inflammation, and causing hormonal imbalance, which collectively contribute to vascular and endothelial dysfunction.[21] Despite these established associations, we found that insomnia was not a significant risk factor for stroke in this study. Therefore, although insomnia is generally considered as a contributor to poor health outcomes, its direct effect on stroke risk may be influenced by other mediating factors or conditions, highlighting the complexity of the etiology of stroke and the multifactorial nature of its risk factors.

In our study, interaction analysis showed that depression did not increase the risk of stroke in the group with insomnia. However, in the group without insomnia, there was a higher stroke risk among individuals with moderate and severe depression compared with those without depression. The lack of stroke risk in the insomnia group could be attributed to insomnia itself affecting stroke risk through various physiological pathways, such as changes in stress hormones, increased inflammatory responses, or autonomic nervous system imbalance, which might overshadow the effect of depression.[5,7] Conversely, in the absence of insomnia, the effect of depression might become more pronounced, particularly with moderate and severe depression potentially imposing a greater burden on the cardiovascular system and thus elevating stroke risk. Therefore, the effects of depression and insomnia on stroke risk are not independent but interrelated, indicating the need to consider their interaction to fully understand their combined effects on stroke risk. Therefore, assessing the combined effects of insomnia and depression is crucial in evaluating stroke risk.

Our findings highlight the nuanced interplay between depression severity and insomnia in influencing stroke risk, providing a theoretical basis for targeted stroke prevention strategies. The findings underscore the importance of personalized medical approaches that consider both mental health and sleep quality, which could ultimately lead to more effective prevention and management of stroke risk.

**Table 4.** Interaction analysis between depression and insomnia on the study outcome

| | Insomnia | | p for interaction |
|---|---|---|---|
| | No | Yes | |
| Depression | | | 0.14 |
| No | 1.00 | 1.00 | |
| Yes | 1.44 (0.92–2.28) | 0.84 (0.46–1.54) | |
| Depression category | | | <0.01 |
| No | 1.00 | 1.00 | |
| Mild | 0.72 (0.33–1.57) | 0.75 (0.34–1.70) | |
| Moderate | 2.04 (1.04–4.00) | 0.73 (0.23–2.36) | |
| Severe | 3.01 (1.43–6.31) | 1.20 (0.42–3.38) | |

Our study has several limitations. First, although our study is a prospective cohort study that captures the natural progression of events, it is not as robust as a randomized controlled trial for establishing causal relationships. Second, the reliance on self-reported data for depression and insomnia statuses might introduce biases, potentially leading to inaccuracies in reporting. While depression was measured using the BDI, more information on its reliability and validity specifically within the Korean population would strengthen the study's credibility. Similarly, insomnia was determined based on self-reported physician diagnoses, but further verification through medical records or standardized insomnia assess-

ment tools could reduce potential bias. Ensuring that these measurements are standardized and reliable across all variables would provide more robust support for the study's findings. Third, we did not explore the variations in insomnia patterns, such as duration and severity, which could significantly influence stroke risk. Fourth, although depression was categorized into four levels to provide a nuanced analysis, the simplification into two broad categories may not fully capture the effect of depression on stroke risk. Fifth, despite statistical adjustments, there remains a potential for bias due to unmeasured or unobserved confounding variables. Lastly, given that our dataset is specific to a certain population group, the generalizability of our findings to other populations may be limited, and the observed associations between depression, insomnia, and stroke risk might manifest differently across various groups.

In conclusion, our study demonstrated that moderate-to-severe depression may be a risk factor for stroke without insomnia. The findings highlight the importance of accounting for depression severity in stroke risk assessment and call for further research to explore the complex interplay between sleep disorders and cardiovascular health.

## Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

## Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

## Author Contributions

Conceptualization: Eujene Jung, Hyun Ho Ryu. Data curation: Seok Jin Ryu. Formal analysis: Eujene Jung, Hyun Ho Ryu. Investigation: Eujene Jung, Hyun Ho Ryu. Methodology: Seok Jin Ryu. Project administration: Seok Jin Ryu. Resources: Eujene Jung, Hyun Ho Ryu. Software: Eujene Jung, Hyun Ho Ryu. Supervision: Hyun Ho Ryu. Validation: Eujene Jung. Visualization: Eujene Jung, Seok Jin Ryu. Writing—original draft: Eujene Jung. Writing—review & editing: Eujene Jung, Hyun Ho Ryu.

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None

## REFERENCES


1. Katan M, Luft A. Global burden of stroke. Semin Neurol 2018;38:208-211.
2. Armstrong JR, Mosher BD. Aspiration pneumonia after stroke: intervention and prevention. Neurohospitalist 2011;1:85-93.
3. Ozturk S. Stroke and stroke risk factors as disease burden. Health Risk Anal 2021;4:146.
4. Nowbar AN, Gitto M, Howard JP, Francis DP, Al-Lamee R. Mortality from ischemic heart disease. Circ Cardiovasc Qual Outcomes 2019;12:e005375.
5. Beckett CW, Niklison-Chirou MV. The role of immunomodulators in treatment-resistant depression: case studies. Cell Death Discov 2022;8:367.
6. Pan A, Sun Q, Okereke OI, Rexrode KM, Hu FB. Depression and risk of stroke morbidity and mortality: a meta-analysis and systematic review. JAMA 2011;306:1241-1249.
7. Carney RM, Freedland KE, Veith RC. Depression, the autonomic nervous system, and coronary heart disease. Psychosom Med 2005;67(Suppl 1):S29-S33.
8. Osimo EF, Pillinger T, Rodriguez IM, Khandaker GM, Pariante CM, Howes OD. Inflammatory markers in depression: a meta-analysis of mean differences and variability in 5,166 patients and 5,083 controls. Brain Behav Immun 2020;87:901-909.
9. Ellis C, Grubaugh AL, Egede LE. The association between major depression, health behaviors, and quality of life in adults with stroke. Int J Stroke 2012;7:536-543.
10. Taylor DJ, Lichstein KL, Durrence HH, Reidel BW, Bush AJ. Epidemiology of insomnia, depression, and anxiety. Sleep 2005;28:1457-1464.
11. Wu MP, Lin HJ, Weng SF, Ho CH, Wang JJ, Hsu YW. Insomnia subtypes and the subsequent risks of stroke: report from a nationally representative cohort. Stroke 2014;45:1349-1354.
12. Jackson-Koku G. Beck depression inventory. Occup Med (Lond) 2016;66:174-175.
13. Jonas BS, Mussolino ME. Symptoms of depression as a prospective risk factor for stroke. Psychosom Med 2000;62:463-471.
14. Barlinn K, Kepplinger J, Puetz V, Illigens BM, Bodechtel U, Siepmann T. Exploring the risk-factor association between depression and incident stroke: a systematic review and meta-analysis. Neuropsychiatr Dis Treat 2014;11:1-14.
15. van West D, Maes M. Activation of the inflammatory response system: a new look at the etiopathogenesis of major depression. Neuro Endocrinol Lett 1999;20:11-17.
16. Bonnet F, Irving K, Terra JL, Nony P, Berthezène F, Moulin P. Anxiety and depression are associated with unhealthy lifestyle in patients at risk of cardiovascular disease. Atherosclerosis 2005;178:339-344.
17. Zhao F, Yue Y, Jiang H, Yuan Y. Shared genetic risk factors for depression and stroke. Prog Neuropsychopharmacol Biol Psychiatry 2019;93:55-70.
18. Javaheri S, Redline S. Insomnia and risk of cardiovascular disease. Chest 2017;152:435-444.
19. Jarrin DC, Alvaro PK, Bouchard MA, Jarrin SD, Drake CL, Morin CM. Insomnia and hypertension: a systematic review. Sleep Med Rev 2018;41:3-38.
20. Johnson KA, Gordon CJ, Chapman JL, Hoyos CM, Marshall NS, Miller CB, et al. The association of insomnia disorder characterised by objective short sleep duration with hypertension, diabetes and body mass index: a systematic review and meta-analysis. Sleep Med Rev 2021;59:101456.
21. Morssinkhof MWL, Wiepjes CM, Bosman BW, Kinds J, Fisher AD, Greenman Y, et al. Sex hormones, insomnia, and sleep quality: subjective sleep in the first year of hormone use in transgender persons. Sleep Med 2023;107:316-326.