

Depressive Symptoms and Risk of Acute Stroke

INTERSTROKE Case-Control Study

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Abstract

Background and Objectives

Depression has been reported to be a risk factor of acute stroke, based largely on studies in high-income countries. In the INTERSTROKE study, we explored the contribution of depressive symptoms to acute stroke risk and 1-month outcome across regions of the world, within subpopulations and by stroke type.

Methods

The INTERSTROKE is an international case-control study of risk factors of first acute stroke, conducted in 32 countries. Cases were patients with CT- or MRI-confirmed incident acute hospitalized stroke, and controls were matched for age, sex, and within sites. Standardized questions asked about self-reported depressive symptoms during the previous 12 months and the use of prescribed antidepressant medications were recorded. Multivariable conditional logistic regression was used to determine the association of prestroke depressive symptoms with acute stroke risk. Adjusted ordinal logistic regression was used to explore the association of prestroke depressive symptoms with poststroke functional outcome, measured with the modified Rankin scale at 1 month after stroke.

Results

Of 26,877 participants, 40.4% were women, and the mean age was 61.7 ± 13.4 years. The prevalence of depressive symptoms within the last 12 months was higher in cases compared with that in controls (18.3% vs 14.1%, $p < 0.001$) and differed by region (p interaction < 0.001), with lowest prevalence in China (6.9% in controls) and highest in South America (32.2% of controls). In multivariable analyses, prestroke depressive symptoms were associated with greater odds of acute stroke (odds ratio [OR] 1.46, 95% CI 1.34–1.58), which was significant for both intracerebral hemorrhage (OR 1.56, 95% CI 1.28–1.91) and ischemic stroke (OR 1.44, 95% CI 1.31–1.58). A larger magnitude of association with stroke was seen in patients with a greater burden of depressive symptoms. While preadmission depressive symptoms were not associated with a greater odds of worse baseline stroke severity (OR 1.02, 95% CI 0.94–1.10), they were associated with a greater odds of poor functional outcome at 1 month after acute stroke (OR 1.09, 95% CI 1.01–1.19).

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INTERSTROKE coinvestigators are listed in Appendix 2 at the end of the article.

Glossary

ICH = intracerebral hemorrhage; mRS = modified Rankin scale; OR = odds ratio.

Discussion

In this global study, we recorded that depressive symptoms are an important risk factor of acute stroke, including both ischemic and hemorrhagic stroke. Preadmission depressive symptoms were associated with poorer functional outcome, but not baseline stroke severity, suggesting an adverse role of depressive symptoms in poststroke recovery.

Depression may be causally related to incident cardiovascular disease^{1,2} and, therefore, a potentially modifiable determinant of the global burden of stroke.³⁻⁵ Meta-analyses of prospective cohort studies report a 34% increase in the risk of stroke associated with depression, but these studies were largely conducted in high-income countries.^{6,7} Compared with the association between poststroke depression and poststroke recovery, the association of prestroke depressive symptoms with stroke and poststroke functional recovery has received less attention.⁸

A challenge in international studies, evaluating the association of depression and stroke, relates to regional differences in approaches to screening and diagnosis of depression. Therefore, relying on a prior diagnosis of depression is expected to result in misclassification bias, which may be distributed differently by region and within subpopulations. Moreover, a reliance on history of clinical depression may identify only participants with moderate or severe depression, when there is emerging evidence that depressive symptoms at lower levels than what is typically indicative of clinical depression may be associated with the risk of incident cardiovascular disease.⁷

The INTERSTROKE study offers a unique perspective evaluating whether a self-reported history of depressive symptoms increases stroke risk, exploring the risk among stroke type (ischemic or intracerebral hemorrhage [ICH]). The aim of this subanalysis of the INTERSTROKE study was to evaluate the associations of depressive symptoms with the risk of stroke and the impact of depressive symptoms on poststroke functional recovery, in different populations characterized by age, sex, and region, and to explore causal mediators. Knowledge of these associations and how they differ across geographical barriers will provide key information to help guide population health initiatives aimed at stroke prevention across low-income to high-income countries. We have previously reported on the association between depressive symptoms and stroke in a preliminary report of the first 3,000 patients in the INTERSTROKE study, but in this study, we report the full-sample analysis of the association of depressive symptoms and risk of stroke and their impact on poststroke recovery in an international population.⁹

Methods

The INTERSTROKE is an international case-control study of risk factors of first acute stroke. It has been previously reported in full.¹⁰ Patients (13,392 stroke patients and 13,485 matched controls) were recruited between January 2007 and August 2015. Each case was matched for site, sex, and age with a control. Each control was matched for sex and age (± 5 years) with cases; age matching was extended (± 10 years) for participants older than 85 years. Biological sex was considered a binary variable in this study (response prompts were only male or female). For comparisons of prevalence across distinct subgroups—for example, by region, country, or ethnic group—potential differences in age structure of the populations were accounted for by direct standardization of the frequencies to the overall INTERSTROKE age distribution with a 5-level age stratification factor (younger than 45, 46–55, 56–65, 66–70, and older than 70 years). Cases were patients who presented with first acute stroke, either ischemic or hemorrhagic (with confirmation by CT or MRI brain imaging), enrolled within 72 hours of hospital admission or 5 days of symptom onset. Controls were either community based or hospital based. Hospital-based controls were patients admitted to hospital or those attending an outpatient clinic for disorders or procedures not related to stroke or transient ischemic attack or visitors or relatives of other inpatients (eMethods 1, links. [lww.com/WNL/C664](http://www.lww.com/WNL/C664) and as previously described¹⁰). Stroke severity was measured using the modified Rankin scale (mRS) during recruitment and at 1-month follow-up.¹¹ Scores on the mRS range from 0 to 6, with increasing scores indicating increasing dependency, with a score of 6 representing death.

Measurement of Risk Factors

Standardized questionnaires were used to collect data on baseline demographics, lifestyle stroke risk factors, and characteristics of acute stroke. Information was collected from the participant or proxy or could have been completed by both participant and proxy. Stroke type of ischemic vs hemorrhagic stroke was based on neuroimaging. Physical measurements of weight, height, waist and hip circumferences, heart rate, and blood pressure were recorded in a standardized manner. An mRS score was collected at 3 time points for cases: preadmission, during interview, and at 1-month follow-up (either in person or by phone) and at 1 time point for controls (during interview). Hypertension was defined by self-reported history of hypertension or the composite of self-

reported hypertension or adjusted blood pressure reading of 140/90 mm Hg or higher. Blood pressure in cases was adjusted to account for acute phase effect and described in eMethods 2 (links.lww.com/WNL/C664).

Diabetes mellitus was defined as self-reported diabetes or a hemoglobin A1c of greater than 6.5% (48 mmol/mol) at recruitment. Stress was defined as feeling irritable or filled with anxiety or as having sleeping difficulties because of conditions at work or at home. Locus of control was assessed by responses to a 6-item scale measuring perceived control over what happens at work and in life, positive outlook for the future, perception of fairness, and life changes over the past decade.

Questionnaire Specific to Depressive Symptoms

Self-reported depressive symptoms were collected using a previously validated adaptation of the short form of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* Composite International Diagnostic Interview questionnaire for depression.¹² The questionnaire used has been validated for use in previous international studies that have taken place in international cohorts including China and low-income and middle-income countries.^{13,14} This questionnaire was also used in the global INTERHEART study, which was translated for use across 52 countries.¹⁵ Depressive symptoms were assessed by asking whether the participant had felt sad, blue, or depressed for 2 or more consecutive weeks during the past 12 months. If a participant answered yes, the severity of the depressive symptoms was quantified by a set of 7 yes-no questions: loss of interest in activities, feeling tired, change in weight, trouble sleeping, trouble concentrating, thinking of death, or feeling worthless. The cumulative number of depressive symptoms was calculated for each participant (maximum 7), and we categorized it into mild (1–2 symptoms), moderate (3–4 symptoms), and severe depression (≥ 5). Preadmission and/or in-hospital use of antidepressant or antipsychotic therapy was captured at interview from cases and controls. The structured standardized case report form also asked participants “if they had given up on making big life improvements a long time ago.”

Statistical Analysis

Simple associations were assessed with frequency tables and Pearson χ^2 tests for 2 independent proportions. We used conditional logistic regression matched case-control pairs for primary analysis of all strokes, ischemic stroke, and ICH and used unconditional analyses for subgroup analysis by non-matched variables. Unconditional logistic regression analyses were adjusted for age, sex, and center. Subgroup analysis by sex was matched by age and center, and subgroup analysis by age was matched by sex and center. All conditional analyses were stratified on the matching criteria. Each control was matched for sex and age (± 5 years) with cases; age matching was extended (± 10 years) for participants older than 85 years. A threshold of $p \leq 0.05$ was applied for statistical significance, including subgroup interactions.¹⁶

We adjusted for covariates in 5 sequential models. Model 1 was adjusted for age and matched by sex and center. Model 2 was additionally adjusted for occupation, education, and wealth index. Model 3 (the primary model) was additionally adjusted for diet, physical activity, alcohol, and smoking. Model 4 was in addition adjusted for body mass index, waist-to-hip ratio, hypertension, atrial fibrillation, and diabetes. Model 5 was additionally adjusted for work stress, home stress, and financial stress. Relative risk estimates are reported as odds ratios (ORs) and accompanying 95% CIs. Model 3 was considered the primary model of the association of depressive symptoms and stroke risk because variables included in subsequent multivariable models may have a mediating role. For unconditional multivariable analysis, age, sex and center were included in the model.

A cumulative odds ordinal logistic regression with proportional odds adjusted for age, sex, center, atrial fibrillation, and stroke type was run to determine the effect of depressive symptoms on modified Rankin scale score at baseline and 1 month poststroke. For the postadmission baseline analysis, we additionally adjusted for preadmission mRS, and for the 1-month analysis, we adjusted for initial poststroke mRS. We conducted statistical analysis with the open-source language R, version 3.4.2.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the ethics committees in all participating centers. Written informed consent was obtained from participants or their proxy.

Data Availability

Data from the INTERSTROKE study are available on reasonable request to any interested research group that meets the criteria for access to confidential data. Data requests may be submitted to the INTERSTROKE Study Management Team.

Results

Baseline Demographics

The mean age of cases was 62.2 ± 13.6 years and that of controls was 61.3 ± 13.3 years and similar in those reporting depressive symptoms vs those not reporting symptoms. The prevalence of vascular risk factors, income, education, and other psychosocial variables in cases and controls, with and without depressive symptoms, is summarized in Table 1. Depressive symptoms were more common in female controls than in male controls. Controls with depressive symptoms experienced more frequent periods of stress and had lower locus of control than controls without depressive symptoms ($p < 0.001$). At baseline, 9.7% of controls with depressive symptoms were taking an antidepressant medication compared with 1.6% of controls without depressive symptoms ($p < 0.001$).

Table 1 Cardiovascular Risk Factors, Education, and Other Psychosocial Variables in Cases + Controls by Depressive Symptoms

Characteristic	Cases ^a			Controls		
	No depressive symptoms	Depressive symptoms ^b	<i>p</i> Value ^c	No depressive symptoms	Depressive symptoms ^b	<i>p</i> Value ^c
	No (N = 10,936)	Yes (N = 2,456)		No (N = 11,579)	Yes (N = 1,906)	
Age, y, mean (SD)	62 (13)	62 (14)	0.51	61 (13)	61 (14)	0.98
Sex, n (%)			<0.001			<0.001
Female	4,251 (39)	1,151 (47)		4,488 (39)	965 (51)	
Male	6,685 (61)	1,305 (53)		7,091 (61)	941 (49)	
Education, n (%)			<0.001			<0.001
None	1,854 (17)	293 (12)		1,429 (12)	206 (11)	
1–8	4,174 (38)	737 (30)		3,741 (32)	552 (29)	
9–12	2,830 (26)	691 (28)		3,061 (26)	430 (23)	
Trade school/college/university	2,078 (19)	734 (30)		3,346 (29)	716 (38)	
Occupation, n (%)			<0.001			<0.001
Professional	1,109 (10)	260 (11)		1,926 (17)	339 (18)	
Laborer	3,659 (33)	862 (35)		3,953 (34)	601 (32)	
Housewife/farmer	4,118 (38)	728 (30)		3,522 (30)	523 (28)	
Police/military/business/clerical	1,157 (11)	327 (13)		1,365 (12)	232 (12)	
Disability/social security	264 (2.4)	87 (3.5)		224 (1.9)	78 (4.1)	
Other	626 (5.7)	191 (7.8)		582 (5.0)	128 (6.7)	
Global stress, n (%)			<0.001			<0.001
None or some periods	9,143 (84)	1,439 (59)		10,285 (89)	1,241 (65)	
Several periods or permanent	1,732 (16)	1,007 (41)		1,273 (11)	660 (35)	
Locus of control, n (%)			<0.001			<0.001
No or less control	1,576 (15)	854 (35)		1,390 (12)	533 (28)	
High control	9,234 (85)	1,572 (65)		10,176 (88)	1,362 (72)	
Alcohol history, n (%)			<0.001			<0.001
Never	6,639 (61)	1,255 (51)		7,211 (62)	1,005 (53)	
Former	991 (9.1)	473 (19)		1,165 (10)	363 (19)	
Current	3,293 (30)	722 (29)		3,192 (28)	536 (28)	
Smoking history, n (%)			<0.001			<0.001
Never or former smoker	7,497 (69)	1,825 (74)		8,872 (77)	1,590 (84)	
Current smoker	3,436 (31)	631 (26)		2,703 (23)	313 (16)	
Body mass index, kg/m ² , mean (SD)	25.6 (4.8)	27.0 (5.1)	<0.001	25.4 (4.6)	26.9 (5.4)	<0.001
Waist-to-hip ratio, mean (SD)	0.94 (0.08)	0.94 (0.09)	0.060	0.92 (0.08)	0.92 (0.08)	0.057
History of hypertension or adjusted BP >140/90 mm Hg at admission, n (%) ^d	7,872 (72)	1,851 (75)	<0.001	5,284 (46)	1,099 (58)	<0.001
Cholesterol, mean (SD)	4.68 (1.23)	4.69 (1.33)	0.85	4.80 (1.19)	4.81 (1.23)	0.91
LDL cholesterol, mean (SD)	2.89 (1.02)	2.86 (1.09)	0.10	2.88 (0.97)	2.83 (1.03)	0.024
HDL cholesterol, mean (SD)	1.11 (0.37)	1.10 (0.37)	0.76	1.17 (0.39)	1.16 (0.40)	0.16

Continued

Table 1 Cardiovascular Risk Factors, Education, and Other Psychosocial Variables in Cases + Controls by Depressive Symptoms (*continued*)

Characteristic	Cases ^a			Controls		
	No depressive symptoms	Depressive symptoms ^b	p Value ^c	No depressive symptoms	Depressive symptoms ^b	p Value ^c
	No (N = 10,936)	Yes (N = 2,456)		No (N = 11,579)	Yes (N = 1,906)	
History of diabetes or HbA1c $\geq 6.5\%$, n (%)	3,016 (28)	742 (30)	0.008	2,503 (22)	453 (24)	0.033
History of atrial fibrillation/flutter, n (%)	1,004 (9.2)	311 (13)	<0.001	302 (2.6)	68 (3.6)	0.017
Taking an antidepressant preadmission, n (%)	153 (1.4)	185 (7.5)	<0.001	181 (1.6)	185 (9.7)	<0.001
Taking an antipsychotic preadmission, n (%)	63 (0.6)	32 (1.3)	<0.001	74 (0.6)	32 (1.7)	<0.001

Abbreviations: BP = blood pressure; CIDI = Composite International Diagnostic Interview; *DSM-IV* = *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Data were missing in 8 participants in western Europe, North America, and Australia, 2 participants in South America, and 4 participants in south Asia for current smoking; 260 participants in western Europe, North America, and Australia, 128 participants in eastern and central Europe and Middle East, 147 participants in South America, 116 participants in southeast Asia, 48 participants in south Asia, and 20 participants in Africa for waist-to-hip ratio; 5 participants in western Europe, North America, and Australia, 2 participants in South America, 3 participants in China, 1 participant in southeast Asia, 1 participant in south Asia, and 6 participants in Africa for physical activity; and 20 participants in western Europe, North America, Australia, 5 participants in South America, 1 participant in southeast Asia, and 1 participant in south Asia for alcohol. These individuals were excluded from the denominator in percentage calculations.

^a Case report forms were completed by cases in 5,573, proxy in 4,967 and by both case and proxy together in 2,918.

^b Depressive symptoms were assessed using the *DSM-IV* CIDI by asking whether the participant had felt sad, blue, or depressed for 2 or more consecutive weeks during the past 12 months.

^c Wilcoxon rank sum test; Pearson χ^2 test.

^d BP in cases was adjusted to account for acute phase effect (eMethods 2, links.lww.com/WNL/C664).

Association of Preadmission Depressive Symptoms With Acute Stroke

Depressive symptoms were more common in cases (18%) than in controls (14%), with a significantly greater univariate odds of all stroke (OR 1.49, 95% CI 1.38–1.61), ischemic stroke (OR 1.48, 95% CI 1.36–1.62), and ICH (OR 1.46, 95% CI 1.25–1.71) among those reporting feeling sad, blue, or depressed for more than 2 weeks or more in the past year. On multivariable analysis (model 3), preadmission depressive symptoms were associated with a significantly greater odds of

all stroke (OR 1.46, 95% CI 1.34–1.58), ischemic stroke (OR 1.44, 95% CI 1.32–1.58), and ICH (OR 1.56, 95% CI 1.28–1.91). The OR for stroke was higher among those in the sample with matched community controls than those with matched hospital-based controls (OR 1.63; 95% CI 1.45–1.84 vs 1.31; 95% CI 1.17–1.47) (eTable 1, links.lww.com/WNL/C664). Additional adjustments for work stress, home stress, and financial stress resulted in attenuation of the estimates for ICH (OR 1.22, 95% CI 0.78–1.91), but there was no detectable change in the association of depressive symptoms

Table 2 Univariable and Multivariable Conditional Logistic Regression of Association Between Depressive Symptoms and Stroke Type

Different models	Depressive symptoms		
	All stroke OR (95% CI)	Ischemic stroke OR (95% CI)	ICH OR (95% CI)
Univariable model (model 1)	1.49 (1.38–1.61)	1.48 (1.37–1.61)	1.55 (1.29–1.85)
Model 2	1.49 (1.38–1.62)	1.48 (1.36–1.62)	1.58 (1.30–1.93)
Model 3 (primary model)	1.46 (1.34–1.58)	1.44 (1.32–1.58)	1.56 (1.28–1.91)
Model 4	1.43 (1.31–1.57)	1.38 (1.25–1.53)	1.73 (1.38–2.17)
Model 5	1.31 (1.08–1.58)	1.36 (1.10–1.68)	1.22 (0.78–1.91)

Abbreviation: OR = odds ratio.

Univariable model (model 1): Univariable base model matched for age, sex, and center.

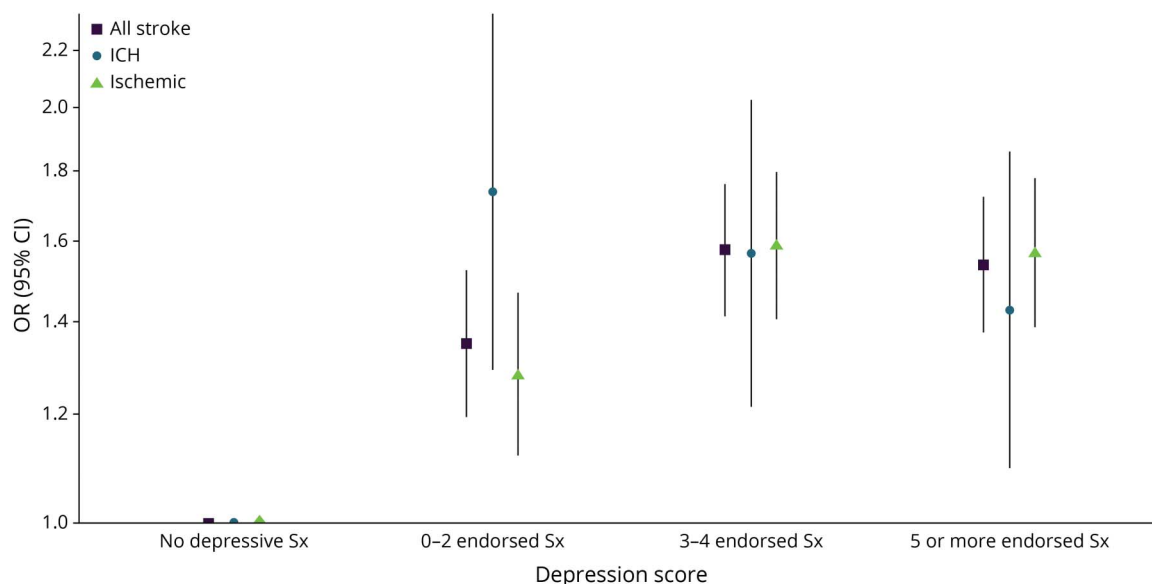
Model 2: Univariable model with adjustment for occupation, education, and wealth index.

Model 3 (primary model): Univariable model with adjustment for occupation, education, wealth index, diet, physical activity, alcohol, and smoking.

Model 4: Univariable model with adjustment for occupation, education, wealth index, diet, physical activity, alcohol, smoking, body mass index, waist-to-hip ratio, hypertension, atrial fibrillation, and diabetes mellitus.

Model 5: Univariable model with adjustment for occupation, education, wealth index, diet, physical activity, alcohol, smoking, body mass index, waist-to-hip ratio, hypertension, atrial fibrillation, diabetes mellitus, work stress, home stress, and financial stress.

Figure 1 Forest Plot of Cumulative Depressive Symptoms and Risk of Stroke



Risk of stroke in those with depressive symptoms in comparison with those without depressive symptoms, stratified according to cumulative burden of depressive symptoms in comparison with those without depressive symptoms. ICH = intracerebral hemorrhage; OR = odds ratio.

with a higher odds of all stroke (OR 1.31, 95% CI 1.08–1.58) and ischemic stroke (OR 1.36, 95% CI 1.10–1.68) (Table 2).

A stratified analysis by the number of endorsed questions in the depression questionnaire demonstrated a greater magnitude of association, moving from mild depressive symptoms (less than 3 questions endorsed) (OR 1.35, 95% CI 1.19–1.53) to moderate depressive symptoms (3–4 questions endorsed) (OR 1.58, 95% CI 1.41–1.75) and severe depressive symptoms (5 or more depressive symptoms endorsed) (OR 1.54, 95% CI 1.38–1.72) (Figure 1).

In participants who were asked whether they had given up on making life improvements a long time ago, a greater odds of stroke was also seen for those reporting having “given up on making life improvements a long time ago” (OR 1.15, 95% CI 1.07–1.24), with a stronger association noted in those with concomitant recent depressive symptoms (OR 1.75, 95% CI 1.53–1.99) (eTable 2, [links.lww.com/WNL/C664](https://www.lww.com/WNL/C664)).

Association by Region

The frequency of depressive symptoms and antidepressant use by region and for cases and controls is shown in Figure 2. South America had the highest frequency of depressive symptoms in both cases and controls, while Southeast Asia had the lowest frequency of depressive symptoms. Antidepressant use was highest in Western Europe/North America/Australasia. There was regional variation in the odds of stroke, with the highest OR for stroke seen in South America (OR 2.18, 95% CI 1.79–2.67) and the lowest OR seen in those from Africa (OR 0.69, 95% CI 0.54–0.86) (p interaction < 0.001) (eTable 1, [links.lww.com/WNL/C664](https://www.lww.com/WNL/C664)). There was no significant difference across regions when comparing hospital-recruited controls and community-

recruited controls. A sensitivity analysis by country income level demonstrated variation across country income level but a consistent association between depressive symptoms and stroke across all country income levels (eTable 3).

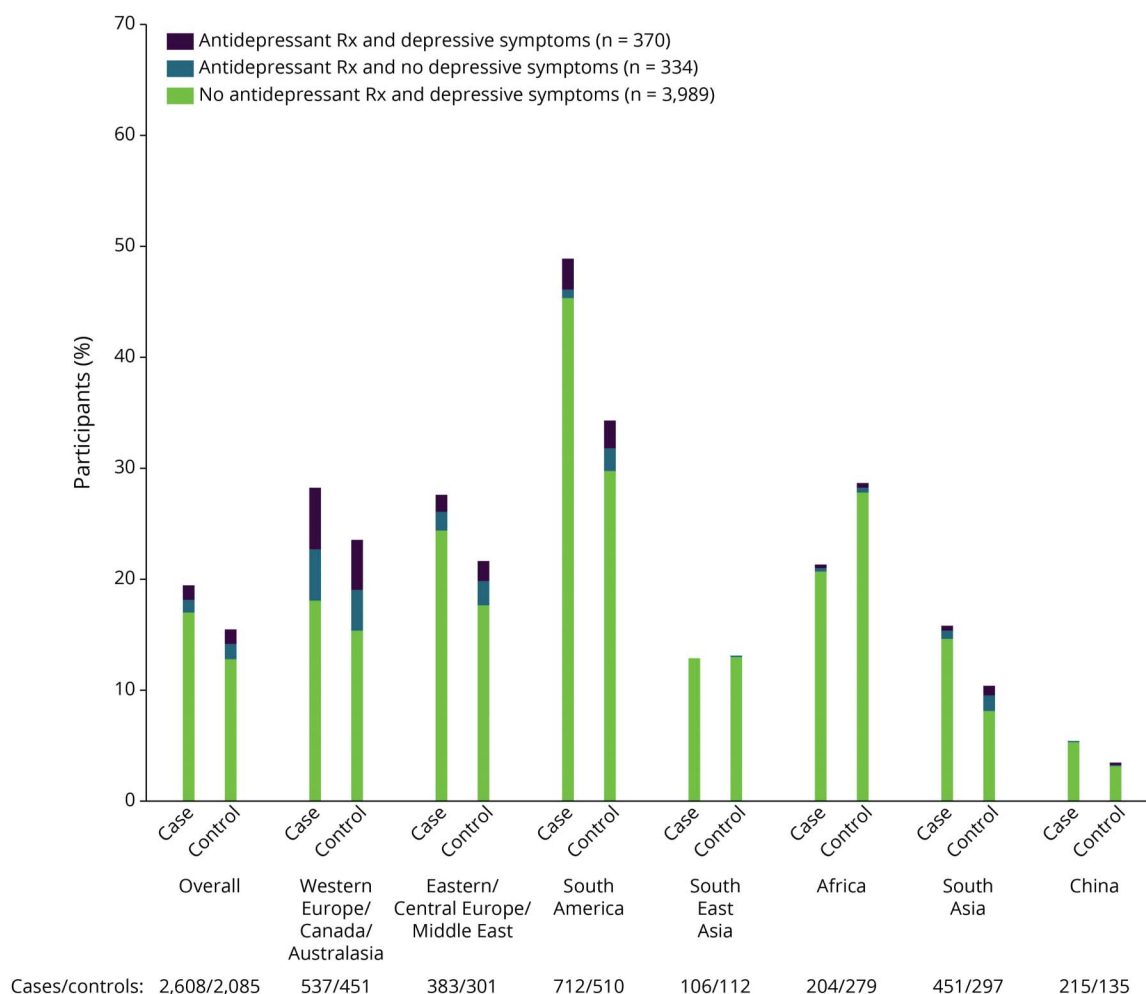
Subgroup Analysis

In subgroup analysis by sex, there was a higher association between depressive symptoms and the risk of stroke in men (OR 1.60, 95% CI 1.43–1.79) compared with that in women (OR 1.31, 95% CI 1.16–1.47) (p interaction = 0.02) (Table 3). There was a higher magnitude of association in patients without hypertension (OR 1.60, 95% CI 1.41–1.81) in comparison with patients with hypertension (OR 1.32, 95% CI 1.21–1.45) (p interaction < 0.001). Depressive symptoms were associated with higher OR of stroke in patients with low stress (OR 1.45, 95% CI 1.33–1.58) compared with those with higher stress 1.17 (1.02–1.33) (p interaction = 0.008), and a differential effect was noted in patients with high locus of control (OR 1.64, 95% CI 1.42–1.90) in comparison with those with low locus of control (OR 1.36, 95% CI 1.25–1.48) (p interaction = 0.03). There was a significant interaction between depressive symptoms and antidepressant medication use with no increase in odds of stroke noted among patients who had depressive symptoms and were taking antidepressant medications. Use of a proxy responder did not materially alter findings.

Association of Preadmission Depressive Symptoms and mRS at 1 Month

There was no significant difference in baseline distribution of mRS between those with depressive symptoms and those without depressive symptoms (p = 0.35), while there was a significant difference in the 1-month distribution of mRS between those with depressive symptoms and those without

Figure 2 Depressive Symptoms and Antidepressant Medication Use by Region for Cases and Controls



Antidepressant medication use and prevalence of depressive symptoms in cases and controls by geographic region.

depressive symptoms ($p < 0.001$). Those with depressive symptoms did not have a significantly greater adjusted OR for 1 point worse on the mRS at baseline (OR 1.02, 95% CI 0.94–1.10), while the adjusted OR for 1 point worse on the mRS at 1 month in those with depressive symptoms was 1.09 (95% CI 1.01–1.19) (Figure 3). Those with depressive symptoms were also more likely to die during the first month after stroke (10% vs 8.1%, $p = 0.003$).

Discussion

In this analysis of 26,877 cases and controls, across 32 countries, self-reported depressive symptoms in the past 12 months were associated with a greater odds of acute stroke. This association was largely consistent across different geographic regions and different age groups but was stronger in men than women and in those without hypertension. Preadmission depressive symptoms were not associated with increased stroke severity on admission but were significantly associated with poorer functional outcomes at 1 month and higher mortality.

We found that the prevalence of prestroke depressive symptoms in the INTERSTROKE study mirrored previous estimates¹⁷ and that our findings of greater stroke risk were generally consistent with findings from previous prospective cohort studies.^{6,18} Previous research focusing on stroke and depression have largely been confined to higher-income countries, while we offer a more international overview with representation from 32 countries. Our findings build on the existing observations that there is an association between depressive symptoms across the spectrum of low mood and subsequent risk of major cardiovascular disease events.^{7,19} Our results extend these observations by further quantifying the contribution of depressive symptoms to the global burden of both ischemic and hemorrhagic stroke and demonstrating that there seems to be a threshold effect with 3 or more depressive symptoms are present. Furthermore, we extend the knowledge base that prestroke depressive symptoms predict worse outcomes on the mRS at 1 month poststroke and higher mortality rates.

Prevalence of depressive symptoms varied among regions, largely consistent with the spread of depressive symptoms that

Table 3 Association Between Depressive Symptoms and Odds of Stroke: Subgroup Analysis^a

	Depressive symptoms (yes/no)	Odds ratio (95% CI)		Depressive symptoms (yes/no)	Odds ratio (95% CI)	p Interaction
Male	No	1.0	Female	No	1.0	0.016
	Yes	1.60 (1.43–1.79)		Yes	1.31 (1.16–1.47)	
Age >65	No	1.0	Age <65	No	1.0	0.64
	Yes	1.49 (1.32–1.68)		Yes	1.44 (1.29–1.60)	
Atrial fibrillation	No	1.0	No atrial fibrillation	No	1.0	0.06
	Yes	1.57 (1.15–2.17)		Yes	1.46 (1.35–1.57)	
Hypertension	No	1.0	No hypertension	No	1.0	<0.001
	Yes	1.32 (1.21–1.45)		Yes	1.60 (1.41–1.81)	
Antidepressant medication use	No	1.0	No antidepressant medication use	No	1.0	0.01
	Yes	0.99 (0.70–1.38)		Yes	1.53 (1.42–1.65)	
Antipsychotic medication use	No	1.0	No antipsychotic medication use	No	1.0	0.69
	Yes	1.27 (0.58–2.77)		Yes	1.48 (1.38–1.59)	
High stress	No	1.0	Low stress	No	1.0	0.008
	Yes	1.17 (1.02–1.33)		Yes	1.45 (1.33–1.58)	
Low control	No	1.0	High control	No	1.0	0.03
	Yes	1.36 (1.25–1.48)		Yes	1.64 (1.42–1.9)	

^a Subgroup analyses were adjusted for variables included in the primary multivariable model (model 3). Subgroup analyses of age and sex were conditional logistic regression adjusted for sex and center or age and center, respectively. All other subgroup analyses were unconditional analyses adjusted for age, sex, center, and variables from the primary multivariable model.

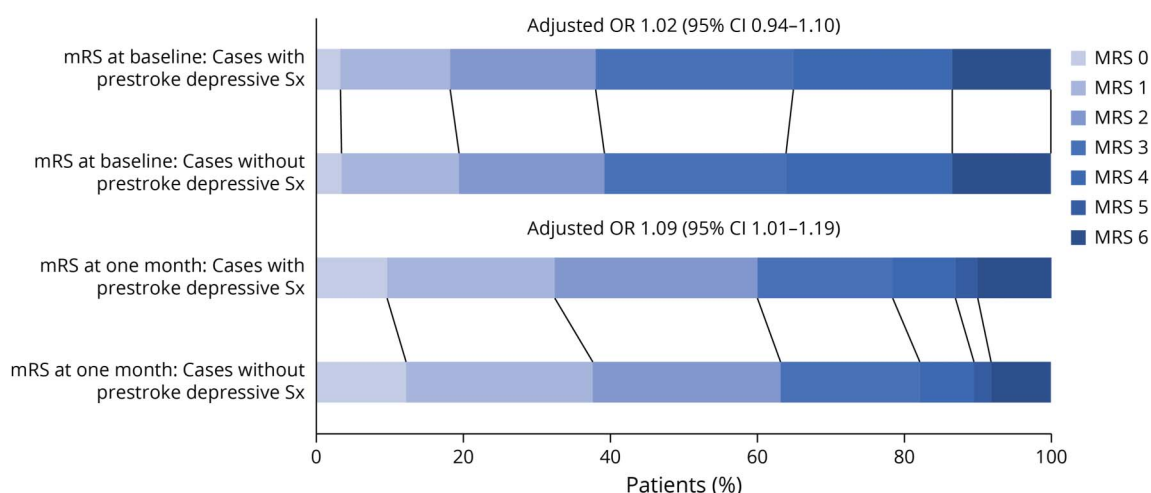
have been reported across the spectrum of cardiovascular disease.^{15,20,21} The lowest rate of depressive symptoms was noted in China and South Asia, but the differences in rates of depressive symptoms could be attributable to variations in the interpretation of the screening questions in different cultures, with well-recognized cross-national differences in depressive symptom reporting.^{22,23} China reported the lowest prevalence of depressive symptoms in keeping with the theory that Chinese tend to deny depression or express it somatically.²⁴ There was still a significant association with acute stroke, suggesting a true phenotype of a patient with depression is being captured here. By contrast, Africa had a high prevalence of depressive symptoms, but there was not a significant association between depressive symptoms and stroke, suggesting that there may be regional variations in the interpretation of depression constructs.⁵ It has been acknowledged that there may be differences in depressive symptom reporting across countries,^{22,23} but this may be more apparent when screening for depression in African populations, with reduced sensitivity of general screening tools for depression in African populations.²⁵ It is also possible that our results may represent a chance qualitative interaction in the African population.²⁶

The association of depression and stroke was largely consistent across different multivariable models, except for the model

including work stress, home stress, and financial stress. This resulted in some attenuation of the association between depressive symptoms and intracerebral hemorrhage, with a significant effect present for ischemic stroke, and this same distinction was noted as the number of depressive symptoms reported increased. Depressive symptoms had a lesser association with stroke in those with high stress than those with low stress. Further exploration of this relationship in a prospective cohort design such as in the PURE study, which has captured both psychological stress and depressive symptoms in a similar manner to the INTERSTROKE study, would be useful in examining the interplay between these 2 constructs further.²⁰

In an effort to identify patients with more chronic positive or negative perspectives in the future, patients were asked about whether they had given up on making life improvements. In this study, we found a higher magnitude of stroke risk when recent depressive symptoms were present alongside an endorsement of this question. This may represent a more chronic phase of anhedonia, and identifying such a distinction is important because those with this type of personality may be successfully targeted with psychological interventions.²⁷ Recent studies have demonstrated that patient-centered, self-directed rehabilitation can improve quality of life and functional outcomes

Figure 3 Distribution of mRS Cases by Depressed vs Not Depressed Groups



Percentage distribution of mRS scores in those with and without depressive symptoms at baseline and at 1 month. Cumulative odds ordinal logistic regression with proportional odds adjusted for preadmission mRS, age, sex, center, atrial fibrillation, and stroke type. A total of 13,460 cases were included in the baseline mRS analyses, and 13,368 cases were included in the 1-month mRS analysis. mRS = modified Rankin scale; OR = odds ratio

poststroke,²⁸ and such targeted interventions would be promising options when exploring therapeutic options in patients presenting with a more chronic pattern of low mood.

The risk of stroke was greater across different levels of depressive symptoms, with a plateau noted in the risk after 3 or more depressive symptoms were endorsed. Awareness of such a threshold effect is important when considering treatment options for subclinical depression in those at risk of cardiovascular disease. There is a lack of evidence for the use of antidepressant medication in subclinical depression, but there is some evidence that psychotherapy may be an effective option.^{29,30} Psychological therapy may also reduce cardiac mortality in those with coronary heart disease,³¹ but uncertainties exist in the quality of evidence at present, and whether this benefit extends to a population with stroke needs further examination.

In subgroup analysis, we found that in patients with recent depressive symptoms and antidepressant medication use, there was no significant association between depressive symptoms and stroke. While the absolute number of patients who were taking antidepressant medication was small, this may suggest that the higher odds of stroke associated with depressive symptoms may be attenuated if the patient is on appropriate treatment. However, care is needed with the use of these medications because there is the potential for harm,³² and this warrants further exploration in a population with larger number of patients on antidepressant medication.

We found that there was no difference in the distribution of immediate poststroke mRS scores among patients with and without depressive symptoms, but rather prestroke depressive symptoms resulted in poorer poststroke recovery at 1 month. This is consistent with previous studies, which have demonstrated that prestroke depressive symptoms are associated

with worse functional outcomes.^{8,33} Previous analyses have just included dichotomized mRS analysis or reported on functional outcomes such as the Barthel index, while our shift analysis provides further quantification of the contribution that prestroke depression makes to poststroke functional outcomes.^{33,34}

An increased awareness of the interplay between prestroke depressive symptoms and differential functional outcomes poststroke is important when considering targeted interventions to enhance strategies for encouraging participation in poststroke rehabilitation. Antidepressant usage poststroke has not been demonstrated to benefit poststroke functional recovery,^{35,36} even in secondary analysis of those with clinical depression,³⁷ and has the potential for harm,^{32,36} so it should not be encouraged routinely. We would suggest that alternative clinical trial approaches such as targeting patients with recent depressive symptoms are needed to see if this can improve poststroke outcomes for patients. More information is needed on whether psychological interventions combined with targeted rehabilitation might be beneficial in patients with recent depressive symptoms.

There are some potential limitations with the INTERSTROKE study. This analysis focused on depressive symptoms assessed at a single baseline examination, meaning cumulative depression burden could not be explored. The questionnaire captured depressive symptoms rather than being a full diagnostic interview with the potential for misclassification that may have underestimated true associations. We asked only about depressive symptoms occurring over the last year, and this may have underestimated depression ascertainment, with known ambiguities and confusion about the concept of depression.³⁸ However, the question about giving up on making life improvements may reflect a more chronic pattern of low mood, and it was also

significant for greater stroke risk. A stroke may differentially influence recollection of past depressive symptoms, but there was no material difference in the odds of stroke among participants who did or did not use a proxy responder, providing empirical evidence that recall bias is not likely to be a contributing factor.

The inclusion of populations across different regions could introduce scope for bias due to different culturally determined mental health perceptions, though our findings though were broadly concordant across multiple regions, particularly when considering diverse approaches such as assessment of symptom burden across country income level. Because this was a case-control study, confounding factors are a potential alternative explanation for the observed positive relationship between depression and stroke risk. Stress did seem to diminish the magnitude of association between depression and ICH, but if it is a confounder, it would only seem to be so for ICH because the estimates remained significant for all stroke and ischemic stroke. All sites were encouraged to recruit cases that were seen in emergency departments and ambulatory clinics, but most cases were patients admitted to hospital. While this does introduce a potential selection bias by reducing the proportion of minor strokes, a further limitation is that it was not feasible to identify all outpatient strokes at many sites.

Our study indicates that depressive symptoms are associated with a larger odds of acute ischemic and hemorrhagic stroke. Our study is unique in having evaluated different constructs of what constitutes depression, including both self-reported symptoms, giving up on making life improvements, and objective constructs such as those on antidepressant treatment during index stroke. We have shown that the effects of depressive symptoms on stroke are similar in people of various ages and across different geographic regions. Considering the increasing global burden of depression, the importance of depression is likely much more important than commonly recognized and may contribute to a substantial proportion of acute stroke presentations and contribute to worse poststroke outcomes.

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Appendix 1 (continued)

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Appendix 1 (continued)

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Continued

Appendix 2 (continued)

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