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Gender Differences in the Risk of Depression in Community-Dwelling Stroke Survivors Compared to the General Population without Stroke

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This study examined the gender-specific association between stroke status and depression in South Korea. A total of 5,746 men and 7,608 women aged ≥30 years who participated in the 2014, 2016, and 2018 Korea National Health and Nutrition Examination Survey were included in the analysis. The cross-sectional surveys targeted the general population consisting of nationally representative adults (≥19 years) residing in Korea. A 9-item Patient Health Questionnaire score of 10 or more was regarded as depression. A higher risk of depression in stroke survivors compared to the non-stroke population was not observed in men (odds ratio [OR], 1.51; 95% confidence intervals [CI], 0.82-2.81), while it was observed in women (OR, 2.49; 95% CI, 1.64-3.77). Compared to non-stroke women, women stroke survivors with a younger age at diagnosis (<60 years) (OR, 4.05; 95% CI, 2.28-7.20) and stroke with duration of ≥10 years (OR, 3.12; 95% CI, 1.63-5.97) had a higher risk for depression. Gender aspects should be more intensively considered in the association between stroke status and depression in community settings.

Key Words: *Gender Identity; Stroke; Depression*

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INTRODUCTION

Globally, stroke is the second leading cause of death and the third most common cause of disability.[1] Depression is a common and serious neuropsychological complication of stroke.[2] About one-third of stroke survivors suffer from depression after stroke.[3] Post-stroke depression affects functional outcomes, rehabilitation results, and mortality.[4-6] Post-stroke depression reduces the quality of life in stroke patients and increases the burden on the family and society.[7]

Although previous studies have reported the higher prevalence of depression in stroke survivors,[8,9] there was insufficient information on whether community-dwelling stroke survivors have a greater risk of depression compared to the non-stroke general population. Moreover, there is little consensus about gender difference in relation to post-stroke depression. Few studies have been conducted to evaluate gender differences in the risk of post-stroke depression compared to those without stroke in a community-dwelling population. Therefore, this study examined the association between stroke status and depression by gender using a representative nationwide sample of the Korean population.

MATERIALS AND METHODS

A total of 5,746 men and 7,608 women aged ≥30 years who participated in the 2014, 2016, and 2018 (January to December respectively) Korea National Health and Nutrition Examination Survey (KNHANES) were included in the final analysis. KNHANES is a nationwide cross-sectional survey conducted annually, and the target population comprises nationally representative civilians residing in Korea.[10] The 9-item Patient Health Question-

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naire (PHQ-9) scale, a commonly recommended screening instrument for depression, was used only in the 2014, 2016, and 2018 KNHANES.[11,12]

Participants' information was collected from health examinations and health interviews. Education level was classified into 4 groups: lower than primary school, middle school, high school, and college or higher. Marital status was dichotomized into married and others (single, divorced, separated, or widowed). Household income was grouped into 4 quartiles: low, moderate-low, moderate-high, and high. Employment status was classified as employed or unemployed (including housewives). Smoking status was categorized as never, former, and current smokers. Alcohol consumption and regular walking activity ($\geq$5 days per week) were dichotomized into yes and no, respectively. Obesity ($\geq$25.0 kg/m^2), hypertension (systolic BP $\geq$140 mmHg or diastolic BP $\geq$90 mmHg or currently being treated), diabetes mellitus (fasting BG $\geq$126 mg/dL or currently being treated), and hypercholesterolemia (total cholesterol level $\geq$240 mg/dL or currently being treated) was also dichotomized into yes and no, respectively.

The total PHQ-9 was based on the response options of 'not at all (0 points),' 'several days (1 point),' 'more than half the days (2 points),' and 'nearly every day (3 points)' for each item. The PHQ-9 score, which ranges from 0 to 27, was dichotomized as normal ($<$10 points) or depression ($\geq$10 points) in this study, because it showed high sensitivity and specificity for major depression.[11] Information on whether a doctor had diagnosed the patients with stroke was obtained. Among stroke survivors, the age at diagnosis of stroke was further identified and the duration of stroke was calculated as the current age minus the age at diagnosis.

Among 14,635 people aged 30 years and older, 1,281 people without information based on PHQ-9 and/or those with missing data on socioeconomic status, health behaviors, and health status were excluded. In total, 13,354 people (5,746 men and 7,608 women) were included in the final analyses. The study was ethically approved by the Institutional Review Board (IRB) of Wonkwang University Hospital (WKUH 2020-07-044).

All statistical analyses were performed separately for men and women, because gender and stroke status have significant interaction ($p<0.05$). The general characteristics were compared based on the presence or absence of stroke using a chi-square test (categorical variables) and the Student's t-test (continuous variables). The prevalence rates of depression were compared according to various indications of stroke status (diagnosis of stroke, age at diagnosis of stroke, and duration of stroke) using a chi-square test. Sequential multiple logistic regression was used to examine the association between stroke classification and depression (PHQ-9 $\geq$10), and odds ratios (OR) and 95% confidence intervals (CI) were calculated. Data were analyzed using IBM SPSS Version 24.0 (IBM Corp., Armonk NY, USA) and p values less than 0.05 were considered statistically significant.

RESULTS

General characteristics of the study population according to diagnosis of stroke by gender are shown in Table 1. Stroke was diagnosed in 160 of the 5,746 men (2.8%) and 162 of the 7,608 women (2.1%). Men and women diagnosed with stroke were older and had lower educational levels, lesser household incomes, and had lower proportions of employment than those without stroke ($p<0.001$). Women diagnosed with stroke were more likely to report unmarried status ($p<0.001$) than those without stroke. Significant differences in health-related behaviors between stroke survivors and non-stroke participants were found in categories including smoking status and alcohol drinking among men, and in alcohol drinking, regular walking activity, and obesity among women ($p<0.05$). The prevalence of hypertension, diabetes mellitus, and hypercholesterolemia were higher in stroke survivors than in non-stroke people in both genders ($p<0.001$).

The prevalence of depression was 8.8% in stroke surviving men and 22.2% in stroke surviving women, which is significantly higher than non-stroke men (3.5%) and non-stroke women (6.5%) (*Ps* <0.001). The prevalence of depression differed significantly according to the diagnosis of stroke and duration of stroke in both men and women (Table 2). After adjusting for age, compared to the non-stroke group, both male and female stroke survivors had a higher risk for depression ([OR, 2.62; 95% CI, 1.46-4.69] and [OR, 3.36; 95% CI, 2.27-4.97]). However, after additional adjustments for related variables, men stroke survivors did not have a higher risk for depression than non-stroke men (OR, 1.51; 95% CI, 0.82-2.81 in model 3), while women stroke survivors had a higher risk for depression than women in the non-stroke group (OR, 2.49; 95% CI, 1.64-3.77 in model 3). Women stroke survivors with young age at diagnosis ($<$60 years) had a higher risk for depression (OR, 4.05; 95% CI, 2.28-7.20 in model 3). In addition, compared to women in the non-stroke group, women stroke survivors with stroke with durations of $<$10 years (OR, 2.19; 95% CI, 1.31-3.67 in model 3) and stroke with durations of $\geq$10 years (OR, 3.12; 95% CI, 1.63-5.97 in model 3) had a higher risk for depression. However, in men, the age at diagnosis of stroke and duration of strokes were not significantly associated with depression in the fully adjusted model (Table 3).

DISCUSSION

This study found a gender difference in the association between PHQ-9-screened stroke and depression. Women with stroke had a 2.49-fold higher risk for depression than women without stroke, but no significant association was observed between stroke diagnosis and depression in men. Moreover, only in women, young age at diagnosis and short duration of stroke may be independent associating factors for depression in this representative Korean national population.

TABLE 1. Characteristics of the study population according to the diagnosis of stroke by gender

	Men			Women		
	Non-stroke (n=5,586)	Stroke (n=160)	p value	Non-stroke (n=7,446)	Stroke (n=162)	p value
Age, years*	54.0 (14.1)	67.3 (9.3)	<0.001	53.7 (13.8)	68.3 (10.6)	<0.001
Education			<0.001			<0.001
Lower than primary school	864 (15.5)	57 (35.6)		1,959 (26.3)	106 (65.4)	
Middle school	632 (11.3)	41 (25.6)		850 (11.4)	25 (15.4)	
High school	1,714 (30.7)	47 (29.4)		2,289 (30.7)	23 (14.2)	
College or higher	2,376 (42.5)	15 (9.4)		2,348 (31.5)	8 (4.9)	
Marital status			0.611			<0.001
Married	4,692 (84.0)	132 (82.5)		5,679 (76.3)	85 (52.5)	
Single/divorced/separated/widowed	894 (16.0)	28 (17.5)		1,767 (23.7)	77 (47.5)	
Household income			<0.001			<0.001
Low	849 (15.2)	78 (48.8)		1,439 (19.3)	79 (48.8)	
Moderate-low	1,382 (24.7)	37 (23.1)		1,866 (25.1)	42 (25.9)	
Moderate-high	1,662 (29.8)	27 (16.9)		2,070 (27.8)	31 (19.1)	
High	1,693 (30.3)	18 (11.3)		2,071 (27.8)	10 (6.2)	
Employment status			<0.001			<0.001
Employed	4,334 (77.6)	63 (39.4)		3,863 (51.9)	37 (22.8)	
Housewives and unemployed	1,252 (22.4)	97 (60.6)		3,583 (48.1)	125 (77.2)	
Smoking status			0.012			0.896
Never-smoker	1,092 (19.5)	30 (18.8)		6,705 (90.0)	145 (89.5)	
Former smoker	2,458 (44.0)	88 (55.0)		385 (5.2)	8 (4.9)	
Current smoker	2,036 (36.4)	42 (26.3)		356 (4.8)	9 (5.6)	
Alcohol drinking			<0.001			<0.001
No	981 (17.6)	51 (31.9)		2,743 (36.8)	92 (56.8)	
Yes	4,605 (82.4)	109 (68.1)		4,703 (63.2)	70 (43.2)	
Regular walking activity			0.150			0.004
No	3,148 (56.4)	81 (50.6)		4,202 (56.4)	110 (67.9)	
Yes	2,438 (43.6)	79 (49.4)		3,244 (43.6)	52 (32.1)	
Obesity			0.704			0.012
No	3,303 (59.1)	97 (60.6)		5,149 (69.2)	97 (59.9)	
Yes	2,283 (40.9)	63 (39.4)		2,297 (30.8)	65 (40.1)	
Hypertension			<0.001			<0.001
No	3,451 (61.8)	48 (30.0)		5,176 (69.5)	45 (27.8)	
Yes	2,135 (38.2)	112 (70.0)		2,270 (30.5)	117 (72.2)	
Diabetes mellitus			<0.001			<0.001
No	4,703 (84.2)	99 (61.9)		6,623 (88.9)	110 (67.9)	
Yes	883 (15.8)	61 (38.1)		823 (11.1)	52 (32.1)	
Hypercholesterolemia			<0.001			<0.001
No	4,491 (80.4)	108 (67.5)		5,607 (75.3)	102 (63.0)	
Yes	1,095 (19.6)	52 (32.5)		1,839 (24.7)	60 (37.0)	

Data are presented as mean (standard deviations)* or number (%). The 9-item Patient Health Questionnaire score dichotomized as normal (<10 points) or depression (≥ 10 points).

Whether women are more vulnerable to depression after stroke is still under debate. A systemic review showed that 7 studies found a significant association between women and post-stroke depression, but 13 studies found no significant association between gender and depression after stroke.[13] A previous meta-analysis of eight studies showed that gender is a risk factor for post-stroke depression in the acute and subacute stages, which was 1.77 times higher in women.[14] A recent follow-up study reported that women stroke survivors, compared to men, were 20% more likely to develop post-stroke depression.[15] However, to date, there are insufficient studies that have assessed whether stroke survivors have a greater prevalence of depression as compared to the general population without stroke, by gender. This study showed that women with strokes had a 2.49-fold higher risk for depression than those without strokes. On the contrary, stroke diagnosis was not a significant predictor for depression in men.

The mechanisms underlying gender differences in depression after stroke are unclear. However, there are sev-

TABLE 2. Stroke status according to depressive symptoms by gender

	Normal (PHQ-9 <10 points)	Depression (PHQ-9 ≥10 points)	p value
Men			
Diagnosis of stroke			<0.001
Non-stroke	5,392 (96.5)	194 (3.5)	
Stroke	146 (91.3)	14 (8.8)	
Age at diagnosis of stroke			0.001
Non-stroke	5,392 (96.5)	194 (3.5)	
Stroke diagnosed at age ≥60 years	70 (93.3)	5 (6.7)	
Stroke diagnosed at age <60 years	76 (89.4)	9 (10.6)	
Duration of stroke			0.002
Non-stroke	5,392 (96.5)	194 (3.5)	
Stroke with duration of <10 years	91 (91.9)	8 (8.1)	
Stroke with duration of ≥10 years	55 (90.2)	6 (9.8)	
Women			
Diagnosis of stroke			<0.001
Non-stroke	6,962 (93.5)	484 (6.5)	
Stroke	126 (77.8)	36 (22.2)	
Age at diagnosis of stroke			<0.001
Non-stroke	6,962 (93.5)	484 (6.5)	
Stroke diagnosed at age ≥60 years	76 (81.4)	16 (17.4)	
Stroke diagnosed at age <60 years	50 (69.4)	20 (28.6)	
Duration of stroke			<0.001
Non-stroke	6,962 (93.5)	484 (6.5)	
Stroke with duration of <10 years	83 (79.0)	22 (21.0)	
Stroke with duration of ≥10 years	43 (75.4)	14 (24.6)	

Data are presented as number (%). PHQ-9: nine-item Patient Health Questionnaire.

eral possible explanations for why women are at greater risk of post-stroke depression. Differential inflammatory responses in the brain after stroke may contribute to the pathogenesis of depression in women as compared to men.[16] Changes in estrogen levels in women may contribute to depression and cognitive decline.[17] In addition, psychosocial factors may also contribute to gender differences. After a stroke, men feel more social pressure not to seek help for depression, whereas women tend to more actively interact with the healthcare system.[18]

Screening for depression in stroke survivors should be recommended, because depression increases cardiovascular mortality in stroke survivors through disruption of autonomic system function, including decreased heart rate variability.[19] After early detection of post-stroke depression, further diagnosis, appropriate management, and necessary referral may also improve outcomes of stroke survivors. Neurologists play an important role in the care and management of stroke patients; hence, they should be familiar with the early detection and treatment of post-stroke depression.[2] Although antidepressants are efficacious for stroke survivors with depression, the majority remains untreated or not appropriately treated with antidepressants.[20] Therefore, periodic clinical attention and ongoing public health interest are needed to identify and treat depression in stroke survivors, particularly women stroke survivors.

Some limitations of this study should be discussed. First, the cross-sectional design makes it difficult to interpret the association as a causal relationship. Second, information about stroke was collected in health interviews, but medical records did not confirm it. Third, only stroke survivors in the community were included in the survey; in-hospital stroke patients with a relatively acute or severe states were excluded. Despite these limitations, this study used well-designed national survey data representative of the Korean population. Moreover, depression was determined using a reliable and validated instrument for measuring depressive symptoms and making criteria-based diagnoses of depression in primary care.

In the community-dwelling population, stroke survivors had a higher prevalence of depression than the general population without stroke in women but not in men. Moreover, young age at diagnosis and long duration of stroke were significant risk factors for depression, although only in women. Gender aspects should be more intensively considered in the association between stroke status and depression in community settings. Consistent screening and active treatment for depression in stroke survivors may improve their quality of life. Psychosocial support and interventions for promoting the mental health of community-dwelling stroke survivors are needed, especially for women diagnosed at a young age.

TABLE 3. Gender-specific relationship between stroke status and depression (PHQ-9 score ≥10)

	Model 1	Model 2	Model 3
Men			
Diagnosis of stroke			
Non-stroke	1.00	1.00	1.00
Stroke	2.62 (1.46-4.69)	1.60 (0.87-2.94)	1.51 (0.82-2.81)
Age at diagnosis of stroke			
Non-stroke	1.00	1.00	1.00
Stroke diagnosed at age ≥60 years	1.92 (0.75-4.90)	1.27 (0.49-3.34)	1.22 (0.46-3.23)
Stroke diagnosed at age <60 years	3.25 (1.60-6.60)	1.87 (0.87-4.02)	1.76 (0.81-3.79)
Duration of stroke			
Non-stroke	1.00	1.00	1.00
Stroke with duration of <10 years	2.40 (1.14-5.08)	1.37 (0.62-3.00)	1.33 (0.60-2.92)
Stroke with duration of ≥10 years	2.98 (1.25-7.08)	2.04 (0.82-5.07)	1.86 (0.74-4.69)
Women			
Diagnosis of stroke			
Non-stroke	1.00	1.00	1.00
Stroke	3.36 (2.27-4.97)	2.42 (1.60-3.64)	2.49 (1.64-3.77)
Age at diagnosis of stroke			
Non-stroke	1.00	1.00	1.00
Stroke diagnosed at age ≥60 years	2.25 (1.29-3.94)	1.60 (0.89-2.85)	1.65 (0.92-2.96)
Stroke diagnosed at age <60 years	5.24 (3.08-8.89)	3.94 (2.23-6.97)	4.05 (2.28-7.20)
Duration of stroke			
Non-stroke	1.00	1.00	1.00
Stroke with duration of <10 years	3.14 (1.93-5.11)	2.11 (1.27-3.54)	2.19 (1.31-3.67)
Stroke with duration of ≥10 years	3.77 (2.03-6.99)	3.04 (1.60-5.78)	3.12 (1.63-5.97)

Data are presented as odds ratio (95% confidence interval). PHQ-9: nine-item Patient Health Questionnaire. Model 1 was adjusted for age. Model 2 was adjusted for model 1 in addition to education, marital status, household income, employment status, smoking status, alcohol drinking, and regular walking activity. Model 3 was adjusted for model 2 in addition to obesity, hypertension, diabetes mellitus, and hypercholesterolemia.

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CONFLICT OF INTEREST STATEMENT

None declared.

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