# *Depression in Stroke Survivors: Ten-Year Follow-Up*. Determinants of the Natural Course of Depressive Symptoms in Stroke Survivors in the Netherlands: The SMART-Medea Study

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*Objectives:* Stroke is the second most common cause of death and a major cause of disability. Besides the physical consequences, depressive symptoms are frequent in the aftermath after stroke. Every year, approximately 15 million stroke survivors worldwide are at risk of developing post-stroke depression. In this study we describe the natural course of depressive symptoms in stroke patients over a long-period of time post stroke and identify associated determinants. *Materials and methods:* From the Second Manifestations of ARTerial disease-Memory, depression and aging (SMART-Medea) study, an observational prospective cohort study, we selected patients with cerebrovascular disease, and used the biannually collected data of the Patient Health Questionnaire-9 for depressive symptoms. A score of ≥10 indicated the presence of depressive symptoms. A multinomial logistic regression analysis was used to identify prognostic determinants for courses of depressive symptoms after stroke. *Results:* During a mean follow-up time of 7.9 years, 62% of the 172 participants was never depressed, 19% had a single episode and 19% had recurrent depressive symptoms. Physical function was associated with increased risk for single episode and recurrent depressive symptoms (OR=1.06 [1.01-1.11]). OR's for social, mental and (vascular) comorbidities variables were not significant. Participants' physical function was only measured at baseline. Several relevant variables were not present in this dataset, including information about clinical events during follow-up. *Conclusion:* Nearly 40% of the participants are confronted with depressive symptoms on the long-term. Physical function plays a substantial part for stroke survivors in the development of these symptoms.

**Key Words:** Post stroke depression—Natural course—PHQ-9—Physical function



## Introduction

Stroke is one of the leading causes of mortality and a major cause of disability, due to impairments in functioning, limitations in activities, and restrictions in societal participation.[20] Although these consequences vary widely between stroke survivors, the most common consequences are physical impairments, communication disorders, cognitive and emotional problems, and mood

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Received September 17, 2021; revision received November 28, 2021; accepted December 7, 2021.

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1052-3057/$ - see front matter



https://doi.org/10.1016/j.jstrokecerebrovasdis.2021.106272

disturbances.[13,50] Every year 15 million people suffer from stroke,[30] in the Netherlands, 40.000 patients have a stroke each year[28] Most stroke patients survive the initial illness and the greatest health effect is usually caused by the long-term consequences.[36]

Stroke survivors' initial goal is to recover to their pre-stroke level of functioning.[19] Nevertheless, approximately 50% of the stroke survivors will remain, at least to some extent, permanently dependent on the assistance of others in their daily life.[27,41] This permanent need for assistance negatively affects the psycho-social well-being of stroke survivors.[15] Common psychological consequences after stroke are depressive feelings, fatigue, anxiety- and sleep disorders.[36] Psychosocial consequences, such as depressive symptoms, often hinder optimal recovery from stroke.[18] These depressive symptoms are associated with higher functional dependency, poor prognosis for further recovery, significant loss of quality of life, and higher mortality after 12 months within stroke survivors.[5,9,32,33]

Depressed feelings, reduction of pleasure in activities (anhedonia), diminished concentration and fatigue or loss of energy are examples of depressive symptoms according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V).[1] Many studies describe an increased prevalence of depressive symptoms in the first five years after stroke,[10,25] with a pooled estimate of 31% (95% CI, 28-35%) in all stroke survivors at any time up to five years post-stroke.[26] In comparison, the lifetime prevalence of experiencing depression in the general population is around 20%.[24] Less is known, however, about the prevalence of these symptoms after those first five years post-stroke.[3] One study reported a depression frequency of 19% during a seven year follow−up.[12] A more recent study found a 55% cumulative incidence of depressive symptoms during a 15 year follow-up.[2] Furthermore, from patients with cardiovascular disease it is known that depressive symptoms show various courses over time and 30% of these patients showed an intermittent or chronic course.[32]

There is, however, limited knowledge about the natural courses of depressive symptoms in stroke survivors on the long-term, in particular after the first five years post-stroke.[3] Moreover, factors such as a history of mental disorders, stroke severity, sex and age are known to be associated with depressive symptoms.[4,45] But it is unknown whether these factors are likewise related to long-term depressive symptoms after stroke. Therefore, the aim of our study was to describe the natural course of depressive symptoms in stroke survivors over a long-term period and to identify which prognostic determinants are associated with the various courses of depressive symptoms after stroke.

## Method

### *Study design*

We conducted a secondary data analysis with data collected as part of the Second Manifestations of ARTerial disease-Memory, depression and aging (SMART-Medea) study, an observational prospective cohort study in patients with a history of vascular diseases referred to the University Medical Center Utrecht (UMC Utrecht) in the Netherlands. The SMART-Medea study is an ancillary study to the SMART-MR study,[32] which has been described in further detail elsewhere.[22] For our study, we selected from this cohort all patients (n=192) with a diagnosis related to cerebrovascular diseases, including a diagnosis of Transient Ischemic Attack (TIA), medical diagnosis of stroke at inclusion or a medical history of stroke, regardless of the presence of depressive symptoms at baseline. From this selection of participants, we excluded patients who had less than three follow-up measures of depressive symptoms, in order to determine the course of depressive symptoms over time. The study was approved by the ethics committee of the UMC Utrecht and stated as non-WMO (file number NL45885.041.13). This secondary data-analysis followed the Dutch code for Health Research from the biomedical research community.

### *Measures*

#### Depressive symptoms

The primary outcome is the natural course of depressive symptoms. Depressive symptoms were measured using the Patient Health Questionnaire-9 (PHQ-9). The PHQ-9 is a commonly used screening tool to identify the presence of depressive symptoms in stroke survivors in the past two weeks.[8] The PHQ-9 items are based on the nine DSM-V symptoms for Major Depressive Disorder.[1] The PHQ-9 scores ranges from 0 to 27, with higher scores indicating more severe depressive symptoms.[34] The diagnostic accuracy of the PHQ-9 in stroke survivors is best at a cut-off point of 10.[14,23,37] For describing the natural courses of depressive symptoms, four courses were defined using criteria by Kooistra et al.[32] For this study a change was made in the cut off value Kooistra et al used because of the focus on stroke survivors.

Four courses were distinguished: a) never depressed, defined as having on all time points a PHQ-9 total score below the cut-off point of 10; b) single episode, defined as having one measurement on all time points ≥10; c) intermittent course, defined as >1 episode but less than 75% of the measurements on all time points ≥10; d) chronic course of depressive symptoms, defined as ≥ 75% of the measurements on all time points ≥10. Participants were

asked to fill in the PHQ-9 questionnaires biannually during the time a subject participated in the study. Missing values of PHQ-9 item scores were imputed with the mean score of that independent measurement of the subject if not more than four items were missing. Other variables were not corrected for missing data.

### Independent variables

Data were collected at baseline using a questionnaire concerning a broad range of determinants, including sex (female or male), age (in years), level of education (low, middle or high level of education), marital status ('married/relationship' or 'divorced, widowed or single'), employment ('employed' or 'unemployed, retired or incapacitated'), Body Mass Index (BMI) (continuous scale), physical function (Groningen Activity Restriction Scale-4 (GARS-4), scores 18-72), smoking (pack years), alcohol consumption ('drinker' or 'non-drinker'), history of depressive symptoms (yes or no), life events in previous year (List of Threatening Experiences) (≥1 yes or no), diabetes mellitus type 2 (DM2) (yes or no), hypertension (yes or no), hyperlipidemia (yes or no), cognitive functions (Mini-Mental State Examination (MMSE), scores 0-30) and vascular diseases (abdominal aortic aneurysm, coronary artery disease or peripheral arterial disease) (yes or no). The determinants we selected to use for the current study are known to be related to depression and/or stroke according to the literature.[3,42,48]

### *Statistical analysis*

Statistical analysis was performed using SPSS Statistics 25.0 (IBM Corporation, Armonk, NY, USA).

We a priori calculated the required sample size given a F test (ANOVA) in our main analyses using G*Power 3.1.9.2. Effect size 0.4, α 0.05 and power of 0.80, resulting in a sample size of 76 participants.

Based on PHQ-9 sum scores participants were categorized in one of four groups reflecting different courses of depressive symptoms. The following method was used: scores on the PHQ-9 were dichotomized, sum score <10 = 0 indicating no depressive symptoms and sum score ≥10 = 1, indicating depressive symptoms present. These dichotomous scores were summed over the years per unique participant into a cumulative score. When the cumulative score was 0, participants were categorized in the group 'never depressive symptoms' and with a cumulative score of 1 to 'single episode'. With a cumulative score of >1 the number of measurements was taken into account. When less than 75% of the measurements scored 1, participants were categorized to the group 'intermittent course', and when more than 75% to the group 'chronic course'.

Baseline characteristics of the four courses of depression: a) never depressed; b) single episode; c) intermittent course; d) chronic course of depressive symptoms are presented using descriptive statistics. The continuous variables age, BMI, GARS-4 and MMSE were summarized using mean number and SD, smoking by median and IQR. Categorical variables sex, level of education, marital status, employment, alcohol consumption, history of depressive symptoms, life events, DM2, hypertension, hyperlipidemia and vascular diseases were summarized using numbers with percentages. Numbers of missing data were described for each variable in the baseline table.

Variables were compared between the four different courses of depression. For continuous variables the ANOVA, Kruskal-Wallis or Welch test were performed, depending on homogeneity of variances and sample size. For categorical variables the Fisher's exact test was performed on account of small groups. When a significant difference is found between groups, coincidence is still a possibility. By correcting for the number of tests with a post-hoc analysis, type 1 error is prevented. Significant differences between the groups were analysed through Games-Howell post-hoc tests, to identify which specific group is accountable.

We performed a multinomial logistic regression analysis to calculate odds ratio's (OR) for the association between the different course types of depression and independent variables. The category 'never depressed' was chosen as the reference group for each course of depression.[21] To fulfill the statistical requirements and prevent overfitting the model, we used a 2-step procedure to determine prognostic determinants for depressive symptoms after stroke. All fourteen variables except age and sex were categorized in four groups (Table 1). Group 1 included variables on the social environment, group 2 mental risk factors, group 3 comorbidities and group 4 included vascular comorbidities.

First, the multinomial logistic regression analysis (MLR) was performed for each variable separately. Second MLR

**Table 1.** *Variable groups for two-step analysis.*

| Groups | Variables |
|---|---|
| Group 1: Social | Education level, marital status and employment |
| Group 2: Mental | Life events, history of depression, MMSE[a] and physical function |
| Group 3: Comorbidities | Alcohol, smoking, Diabetes Mellitus type 2 and BMI[b] |
| Group 4: Vascular | Hypertension, hyperlipidemia and vascular comorbidities |

[a]MMSE= Mini Mental State Examination;
[b]BMI= Body Mass Index

was performed for each group of variables separately. To identify significant variables in each of these groups, backward stepwise selection based on a likelihood-ratio test with a P value of 0.1 was used. Third, the determinants which turned out significant in step two were selected for the final model and validated with backward stepwise selection in MLR.

## Results

### *Participants and demographic data*

Of the 192 participants 20 (10.4%) were excluded because of < 3 follow-up measures of the PHQ-9. The mean age of our sample of participants (n=172) was 63.3 (SD 9.8) and 131 (76.2%) were male. At baseline 140 (81.4%) of the participants were married, 125 (72.7%) had a medical history of hypertension and the median smoking pack years was 19.4. At baseline 79 (45.9%) participants reported a medical history of mood disorder or anhedonia. The mean physical function score on the GARS-4 was 21 (SD 8.1). Participants' baseline characteristics are presented in detail in Table 2.

Participants differ in follow-up time, ranging from 1.5 to 10.5 years with an average of 7.9 years (SD 2.4). Further, not all participants filled in the PHQ-9 questionnaire biannually, resulting in variation in number of questionnaires (mean 11.4, range 3-15) (Table 2). Analysis of missing values of all determinants was performed and showed a maximum of 5.8% missing variables per variable, distributed among 16% of the cases. Life events and smoking pack years were responsible for more than half of the missing values. In the long-term data 2.3% of the PHQ-9 measurements were missing.

### *Courses depressive symptoms*

The calculation of the participants' course of depressive symptoms in the years following stroke showed that 107 (62.2%) participants were identified as being never depressed. Within 33 (19.2%) participants a single episode of depressive symptoms was identified. An intermittent course was identified in 24 (14%) participants, and the chronic course of depressive symptoms was identified in 8 (4.7%) participants.

No significant differences were found between courses of depressive symptoms and baseline variables. Except for the level of education and the GARS-4 score (Table 2), but after Games-Howell post-hoc analysis both significant differences were refuted.

### *Multinomial logistic regression*

Few participants (n=8) were identified with a chronic course of depressive symptoms. To perform appropriate statistical analyses, this group was merged with 'intermittent course' (n=24), and renamed as 'recurrent depressive symptoms' (n=32). Univariate multinomial logistic regression analysis (MLR) resulted in OR's per variable (Table 3). Next part of the analysis included the two-step selection of prognostic determinants. Within each group of variables (Table 2), those significantly associated with the course of depression were identified: physical function, alcohol consumption and high education. These variables were entered in the final MLR model and corrected for age and sex. The conditions for the model were satisfied, as tests on tolerance and Variance Inflation Factor showed.

In the final model, MLR analysis showed little differences in variables between the courses of depressive symptoms after stroke. The physical function score on the GARS-4 was a significant determinant for a single episode (OR=1.06 [1.01-1.11]) and recurrent depressive symptoms (OR=1.06 [1.01-1.12]). Alcohol consumption and high education did not remain to significantly explain the course of depressive symptoms (Table 3). Lower level of physical functioning was associated with a single and recurrent course of depressive symptoms compared to no depression.

## Discussion

The aim of our study was to describe the natural course of depressive symptoms in stroke survivors over a long-term period and to identify which prognostic determinants are associated with the various courses of depressive symptoms after stroke. Overall, around 40% of the people in this cohort experienced depressive symptoms at least once during ten years follow-up. Of them, the majority suffered from a single episode, one third had intermittent depressive symptoms and less than a quarter suffered from a chronic course of depressive symptoms. Lower level of physical function at baseline was associated with courses of depressive symptoms after correcting for other variables.

The results in this study endorse that depressive symptoms are a serious problem after stroke. The 40% with a follow-up time of 10 years is comparable with the cumulative incidence of 31% (follow-up 5 y) and 55% (follow-up 15 y) reported earlier,[26,2] and suggest that the cumulative incidence increases over time. It should be noted that these studies are not completely equivalent, Ayerbe et al. uses a screening instrument in a hospital based population, this applies to half of the included studies by Hackett and Pickels, 2014.[26] Nevertheless, it seems the longer stroke survivors are followed over time, the more often depressive symptoms occur. This could be an indication that prevalence of depressive symptoms increases over time. This might be explained by physical functioning.

Our study revealed that baseline physical function is associated with the presence of symptoms of depression over time. This is consistent with literature, where physical impairments were found to be associated with the presence of depressive symptoms in stroke survivors.[4,35]

**Table 2.** *Baseline characteristics on courses of depressive symptoms after stroke.*

| | Total (n=172) | | Never depressed (n=107) | | Single episode (n=33) | | Intermittent (n=24) | | Chronic (n=8) | | P value | Missing (n) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Follow-up in years *mean, range (SD)* | 7.9<br>1.5- 10.5 | (2.4) | 8 | (2.3) | 7,8 | (2.3) | 7.4 | (2.7) | 7.3 | (2.2) | .496[2] | |
| Number of PHQ-9[a] measurements *mean, range (SD)* | 11.4<br>3-15 | (3.8) | 11.8 | (3.8) | 11,2 | (3.6) | 10.5 | (4.4) | 9.4 | (3.8) | .107[2] | |
| Age (years) *mean (SD)* | 63.3 | (9.8) | 63.6 | (9.5) | 63,4 | (11) | 62.3 | (10.7) | 60.9 | (8.2) | .841[1] | 0 |
| Sex, female *n (%)* | 41 | (24) | 23 | (21) | 7 | (21) | 8 | (33) | 3 | (38) | .435[3] | 0 |
| **Social** | | | | | | | | | | | | |
| Level of education *n (%)* | | | | | | | | | | | .029[3]* | 0 |
| Low | 45 | (26) | 25 | (23) | 10 | (30) | 5 | (21) | 5 | (62) | | |
| Middle | 62 | (36) | 33 | (31) | 15 | (46) | 13 | (54) | 1 | (13) | | |
| High Level | 65 | (38) | 49 | (46) | 8 | (24) | 6 | (25) | 2 | (25) | | |
| Marital status *n (%)* | | | | | | | | | | | .601[3] | 0 |
| Married or relationship | 140 | (81) | 87 | (81) | 29 | (88) | 18 | (75) | 6 | (75) | | |
| Divorced, widowed or single | 32 | (19) | 20 | (19) | 4 | (12) | 6 | (25) | 2 | (25) | | |
| Employment *n (%)* | | | | | | | | | | | .532[3] | 0 |
| Employed | 39 | (23) | 28 | (26) | 5 | (15) | 4 | (17) | 2 | (25) | | |
| Unemployed/retired/incapacitated | 133 | (77) | 79 | (74) | 28 | (85) | 20 | (83) | 6 | (75) | | |
| **Mental** | | | | | | | | | | | | |
| Life-events, ≥1 *n (%)* | 94 | (55) | 53 | (50) | 21 | (64) | 16 | (67) | 4 | (50) | .506[3] | 10 |
| History of depressive symptoms *n (%)* | 79 | (46) | 43 | (40) | 18 | (55) | 14 | (58) | 4 | (50) | .221[3] | 2 |
| MMSE[b] *mean (SD)* | 28.5 | (1.7) | 28.5 | (1.6) | 28.8 | (1.2) | 28.2 | (2.5) | 28.3 | (1.3) | .673[2] | 3 |
| GARS-4[c] *mean (SD)* | 21.7 | (8.1) | 20.2 | (5.9) | 23.9 | (10.8) | 24.7 | (10.8) | 23.1 | (8) | .008[2]* | 3 |
| **Comorbidities** | | | | | | | | | | | | |
| Alcohol use *n (%)* | | | | | | | | | | | .104[3] | 2 |
| Non drinker | 51 | (30) | 29 | (27) | 7 | (21) | 12 | (50) | 3 | (37) | | |
| Drinker | 119 | (69) | 77 | (72) | 25 | (76) | 12 | (50) | 5 | (63) | | |
| Smoking (pack years) *median (IQR)* | 19.4 | (29) | 21.8 | (29) | 26 | (32.6) | 16.8 | (28.7) | 10.6 | (23.7) | .551[2] | 10 |
| Diabetes Mellitus type 2 *n (%)* | 35 | (20) | 18 | (17) | 8 | (24) | 6 | (25) | 3 | (38) | .323[3] | 0 |
| BMI[d] *mean (SD)* | 27 | (3.9) | 26.8 | (3.3) | 27.9 | (4.1) | 26.7 | (5.6) | 27 | (4) | .560[4] | 0 |
| **Vascular** | | | | | | | | | | | | |
| Hypertension *n (%)* | 125 | (73) | 78 | (73) | 24 | (72) | 17 | (71) | 6 | (75) | .978[3] | 2 |
| Hyperlipidaemia *n (%)* | 38 | (22) | 24 | (22) | 7 | (21) | 4 | (17) | 3 | (38) | .670[3] | 2 |
| Vascular comorbidities[e] *n (%)* | 64 | (37) | 40 | (37) | 13 | (39) | 9 | (38) | 2 | (25) | .939[3] | 0 |

[a]PHQ-9= Patient Health Questionnaire 9;
[b]MMSE= Mini Mental State Examination;
[c]BMI= Body Mass Index;
[d]GARS-4= Groningen Activity Restriction Scale 4;
[e]Abdominal aortic aneurysm, Coronary artery disease or Peripheral arterial disease;
[1]ANOVA test.
[2]Kruskal-Wallis
[3]Fisher's exact test,
[4]Welch test;*P value below .05

**Table 3.** *Univariate multinomial logistic regression analysis on courses of depressive symptoms after stroke.*

| | Never is the reference category | | | |
|---|---|---|---|---|
| | Single episode[a] | | Recurrent episodes[a] | |
| | OR | 95% CI | OR | 95% CI |
| Age (years) | 1.00 | (0.96-1.04) | 0.98 | (0.94-1.02) |
| Sex | 1.02 | (0.39-2.64) | 0.52 | (0.22-1.24) |
| **Social** | | | | |
| Level of education | | | | |
| Middle vs Low | 0.54 | (0.24-1.19) | 0.57 | (0.26-1.29) |
| High vs Low | 2.64* | (1.09-6.38) | 2.53* | (1.05-6.15) |
| Marital status | 1.67 | (0.53-5.28) | 0.69 | (0.27-1.76) |
| Employment | 0.50 | (0.18-1.43) | 0.65 | (0.24-1.75) |
| **Mental** | | | | |
| Recent life-events | 0.66 | (0.29-1.48) | 0.58 | (0.25-1.36) |
| History of depressive symptoms | 0.58 | (0.26-1.25) | 0.49 | (0.22-1.11) |
| MMSE[b] | 1.14 | (0.86-1.52) | 0.90 | (0.73-1.11) |
| GARS-4[c] | 1.06* | (1.01-1.11) | 1.06* | (1.01-1.12) |
| **Comorbidities** | | | | |
| Alcohol use | 0.74 | (0.29-1.90) | 2.34* | (1.04-5.29) |
| Smoking (pack years) | 1.00 | (0.98-1.02) | 1.00 | (0.98-1.02) |
| Diabetes Mellitus type 2 | 0.63 | (0.25-1.62) | 0.52 | (0.21-1.30) |
| BMI[d] mean | 1.07 | (0.98-1.18) | 1.00 | (0.90-1.12) |
| **Vascular** | | | | |
| Hyperlipidaemia | 0.99 | (0.38-2.58) | 1.03 | (0.40-2.68) |
| Hypertension | 0.93 | (0.37-2.31) | 1.09 | (0.45-2.64) |
| Vascular comorbidities[e] | 0.92 | (0.41-2.05) | 1.14 | (0.50-2.61) |

[a]Never depressive symptoms is the reference category
[b]MMSE= Mini Mental State Examination;
[c]GARS-4= Groningen Activity Restriction Scale 4;
[d]BMI= Body Mass Index;
[e]Abdominal aortic aneurysm, Coronary artery disease or Peripheral arterial disease;
*P value below .05

People who are less independent in activities in daily living after their stroke, more often suffer from feelings of depression. Subsequently, when these stroke survivors suffer from depressive symptoms their physical activity is likely deteriorate.[43] We know that being active is protective against depression for stroke survivors.[6,35] This applies on the long term as well.[38,39] But most stroke survivors get inactive and in poor condition, and their physical function diminishes with age.[51] This increases the risk for depressive symptoms again. This downward spiral can cause symptoms of depression to persist or even worsen during life.

In our study physical function was found to be associated with single and recurrent episodes of depressive symptoms after stroke. Subgroup analysis resulted in multiple possible determinants; physical function, alcohol consumption and high education. Thereafter, the MLR only showed physical function to be significant. This result is comparable with the meta-analysis and review mentioned earlier, where physical disability and functional dependency were identified as determinants for depression after stroke.[4,35] Our study varied since it did not confirm baseline cognitive impairment to be a prognostic determinant associated with depressive symptoms after stroke.

Physical function was measured with the GARS-4, a non-disease-specific instrument to measure disability in activities of daily living (ADL) and instrumental ADL (IADL).[47] The questionnaire is easy to administer, comprehensive and a valid measure for assessing disability in older people.[31] Notable, participants had surprisingly good physical function at baseline according to the GARS-4. Compared to other studies where stroke survivors report worse physical function.[44] Mean score was 21 on a scale of 18 to 72, where higher scores indicate more serious restrictions.[17] This might partly be caused by the exclusion criteria 'being dependent of others in activities in daily living' that was used in the SMART cohort,[46] inducing a sample which is relatively 'healthy' with regards to physical functioning.

The physical function OR in the multinomial regression is very close to 1, and the question arises about clinical relevance. Several things should be taken into account. The relatively 'good' physical function score at baseline limits us from saying anything so confidently about the found association. But this apparently minor influence of

physical function was calculated by merely one measurement. Literature suggests to interpret such indices as a measure of effect size. To prevent undervaluing the effect, impact should be based on clinical rates as well.[7] According to the current study, a worse GARS-4 score at baseline could make a difference to what extent stroke survivors suffer from depressive symptoms as the years follow. Thus, it emphasizes the importance of early awareness of physical function in patients with arterial disease further.[29,44]

On the other side, the question arises if the association of physical function is higher in reality. A different stroke survivor database, with a lower, but more general, physical function score might have led to a higher OR. Because a reduced level of physical activity over time is found to increase the risk of developing depression relative to remaining active or increasing activity levels.[38] Although stroke survivors are capable of achieving great physical progress with rehabilitation, nevertheless physically deteriorate more as the years follow.[25] We assume that the risk for physical deterioration is equal in all four course type groups. But sicker stroke survivors are more likely to experience poorer health in subsequent years, leading to a greater likelihood of depressive symptoms.[27]

### *Strengths and limitations*

Using an existing database has led to several restrictions concerning interpreting the findings of the study. Our study population consisted largely of men. Partially explainable since the incidence of stroke in men is greater than in women.[49] This may justify why the determinant sex was not significantly associated, compared to previous studies.[16,45] But, sex differences are an important point of attention in stroke, mentioned by Condonnier et al.[11]

The relatively healthy sample with regards to physical function, resulted in that the findings of our study are less generalizable to the general stroke population. In addition, there were no follow-up measurements on physical function. Therefore, we can only say something about the relationship between baseline physical functioning and depressive symptoms. It is important to realize that all variables are measured at baseline only. However, over time many more aspects have influenced the presence of the depressive symptoms that we are unaware of.

Moreover, the time span between participants' stroke and time of answering the baseline questionnaire was unknown. We can therefore describe the study population less precisely. This essential information was missing as well as data about participants' health and life events in the years following. We have no insight into what happened in the following years.

Several relevant variables were not part in this dataset: fatigue, stroke severity (extinction between participants suffering from cerebral hemorrhage, cerebral infarction or TIA) and clinical events (clinical diagnosed depression and clinical events during follow-up). Also, only the level of depressive symptoms could be assessed during follow-up instead of a clinical diagnose of depression. It is thus possible that the absolute percentages are lower since PHQ-9 sensitivity is not perfect for depression diagnosis.[40]

Strength of this study was the long follow-up period up to ten years, since limited research is done on post-stroke depression on the long-term. The frequent measurements of depressive symptoms present a detailed description about the courses over a long-period of time. Furthermore, sample size was relatively large and the response rates during all PHQ-9 follow-up measurements were high. Due to a low number of participants in the chronic and intermittent group, the new group was made. By merging these groups and the two-step method for selecting variables, overfitting was prevented.

More research on the long-term should be done to validate these results and to enable systematic research. Future studies should focus on a different cohort with more extensive and repeating measurements on participants' health. Which can then be used to evaluate and improve current guidelines concerning stroke survivors and physical function.

In conclusion, in this cohort almost 40% of the participants suffers from depressive symptoms at least once during ten years follow-up. A worse physical function at baseline was associated with an increased chance of suffering from depressive symptoms over a long-period of time. The results of this study indicate that post-stroke depression affects more patients on a longer period of time than previously thought. This emphasises the needful attention for physical function in this population where maximum effort should be made for long-term rehabilitation.

## Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Data Statement

The data is unavailable to access since the research data is confidential.

## Authors' contributions

AB was the principal researcher, supervised by JM. AB takes full responsibility for the data, the analysis and interpretation, and the conduct of the research. Together, AB, JM, MIG and IU collaborated in drafting and revising the manuscript and interpretation of the data. All authors contributed to and have approved the final manuscript.

## Declaration of Competing Interest

All authors declare no conflict of interest.

**Acknowledgement:** Many thanks to H. Rasing MSc RN, J. Bokhorst BSc and N. Wouda MSc who provided help concerning writing assistance or proof reading the article.

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